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(54) Title: METHODS FOR THE TREATMENT OF NEOPLASMS

(57) Abstract: The invention features a method for treating a patient having a cancer or other neoplasm by administering to the patient a niclosamide, or a structural or functional analog thereof, and, optionally, one or more antiproliferative agents in an amount effective to inhibit the growth of the neoplasm.

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METHODS FOR THE TREATMENT OF NEOPLASMS

Background of the Invention

The invention relates to the treatment of neoplasms such as cancer.

Cancer is a disease marked by the uncontrolled growth of abnormal cells. Cancer cells have overcome the barriers imposed in normal cells, which have a finite lifespan, to grow indefinitely. As the growth of cancer cells continues, genetic alterations may persist until the cancerous cell has manifested itself to pursue a more aggressive growth phenotype. If left untreated, metastasis, the spread of cancer cells to distant areas of the body by way of the lymph system or bloodstream, may ensue, destroying healthy tissue.

According to a recent American Cancer Society study, approximately 1,268,000 new cancer cases were expected to be diagnosed in the United States in the year 2001 alone. Lung cancer is the most common cancer-related cause of death among men and women, accounting for over 28% of all cancer-related deaths. It is the second most commonly occurring cancer among men and women; it has been estimated that there were more than 169,000 new cases of lung cancer in the U.S. in the year 2001, accounting for 13% of all new cancer diagnoses. While the rate of lung cancer cases is declining among men in the U.S., it continues to increase among women. According to the American Cancer Society, an estimated 157,400 Americans were expected to die due to lung cancer in 2001.

Cancers that begin in the lungs are divided into two major types, non-small cell lung cancer and small cell lung cancer, depending on how the cells appear under a microscope. Non-small cell lung cancer (squamous cell carcinoma, adenocarcinoma, and large cell carcinoma) generally spreads to other organs more slowly than does small cell lung cancer. Small cell lung cancer is the less common type, accounting for about 20% of all lung cancer.

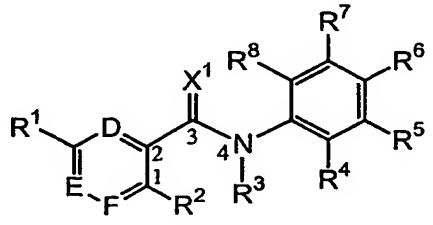
Other cancers include brain cancer, breast cancer, cervical cancer, colon cancer, gastric cancer, kidney cancer, leukemia, liver cancer, lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, sarcoma, skin cancer, testicular cancer, and uterine cancer. These cancers, like lung cancer, are sometimes treated with chemotherapy.

Antiproliferative agents currently in use or in clinical trials include paclitaxel, docetaxel, tamoxifen, vinorelbine, gemcitabine, cisplatin, etoposide, topotecan, irinotecan, anastrozole, rituximab, trastuzumab, fludarabine, cyclophosphamide, gentuzumab, carboplatin, interferon, and doxorubicin. The most commonly used antiproliferative agent is paclitaxel, which is used alone or in combination with other antiproliferative agents such as: 5-FU, doxorubicin, vinorelbine, cytoxan, and cisplatin.

Summary of the Invention

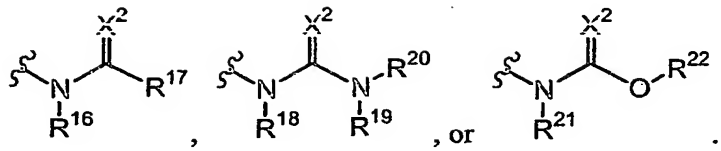
We have discovered that niclosamide, a salicylanilide compound, acts as an antiproliferative agent against cancer cells, and enhances the activity of antiproliferative agents when used in combination therewith. Structural and functional analogs of niclosamide are known and can also be used alone or in combination with antiproliferative agents in the methods of the invention.

Accordingly, the invention features a method for treating a patient who has a neoplasm or is at risk for developing a neoplasm by administering to the patient a compound having formula I:

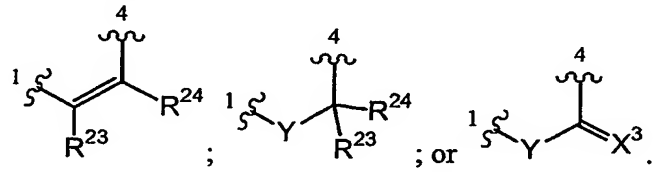


I

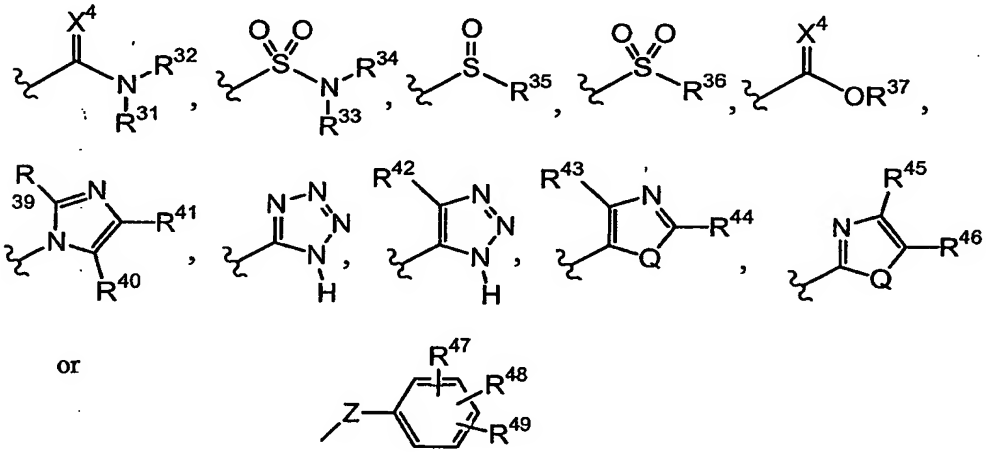
or a salt thereof. In formula I D is N or CR^9; E is N or CR^{10}; F is N or CR^{11}; and R^1 is H, halide, OR^{12}, SR^{13}, $NR^{14}R^{15}$, or described by one of the formulas:



R^2 is H, OH, or OR^{12}; R^3 is H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; or R^2 and R^3 combine to form a six-membered ring in which position 1 is connected to position 4 by one of the groups:



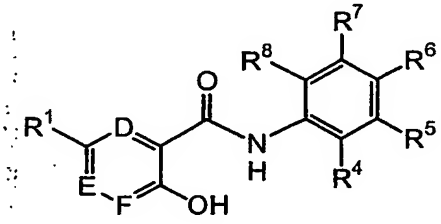
R^4 and R^8 are each, independently, selected from H, halide, CF_3, OR^{28}, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; and R^5, R^6, and R^7 are each, independently, selected from H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl, halide, NO_2, CO_2H, SO_3H, CF_3, CN, OR^{29}, SR^{30}, or are described by the formulas:



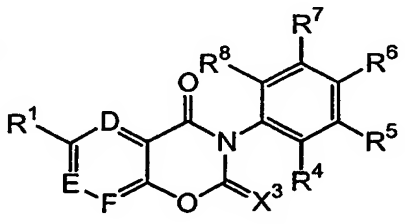
For compounds of formula I, each X^1, X^2, X^3, and X^4 is, independently, O S; or NR^{38}; Y is $CR^{25}R^{26}$, O, S, or NR^{27}; Z is O, S, or $CR^{50}R^{51}$; each Q is, independently, O, S, or NR^{52}; R^9, R^{10}, and R^{11} are each, independently, H, OH, OR^{12}, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-7} heteroalkyl, halide, or NO_2; R^{12}

and R^{13} are each, independently, acyl, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; R^{17}, R^{22}, R^{35}, R^{36}, R^{37}, R^{38}, and R^{52} are each, independently, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; R^{14}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, and R^{47} are each, independently, H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; and R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, and R^{51} are each, independently, H, halide, CN, NO_2, CF_3, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl. The compound of formula (I) is administered in an amount effective to inhibit growth of the neoplasm.

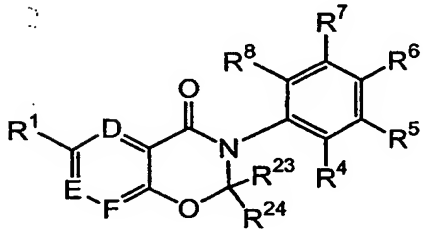
Desirable compounds of formula I are further described by any one of formulas II-V:



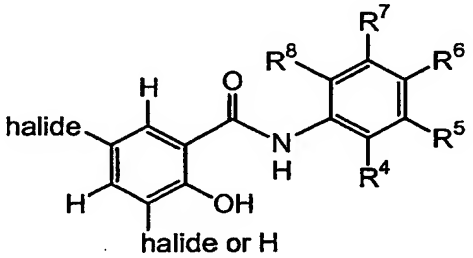
II



III



IV



V

wherein F, E, D, X^3, R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{23}, and R^{24} are as defined above.

Furthermore, the invention features a method for treating a patient having a neoplasm or who is at risk for developing a neoplasm. This method includes the step of administering to the patient a compound selected from the group consisting of niclosamide, oxyclozanide, closantel, rafoxanide, resorantel, clioxanide, tribromsalan, dibromsalan, brotianide, 4'-chloro-3-nitrosalicylanilide, 4'-chloro-5-nitrosalicylanilide, 2'-chloro-5'-methoxy-3-nitrosalicylanilide, 2'-methoxy-3,4'-dinitrosalicylanilide, 2',4'-dimethyl-3-nitrosalicylanilide, 4',5-dibromo-3-nitrosalicylanilide, 2'-chloro-3,4'-dinitrosalicylanilide, 2'-ethyl-3-nitrosalicylanilide, 2'-bromo-3-nitrosalicylanilide, and flusalan (many of which fall within formula I, above), or a salt thereof, in an amount effective to inhibit growth of the neoplasm.

The invention also features a method for treating a patient having a neoplasm or who is at risk for developing a neoplasm. This method includes the step of administering to the patient an antihelminthic agent, or a salt thereof, in an amount effective to inhibit the growth of the neoplasm. Antihelminthic agents, other than salicylanilides, that can be used in the methods of the invention include ivermectin, abamectin, doramectin, moxidectin, mylbemycin D, niclofolan, praziquantel, diamphenethide, and chlorsulon.

For any of the foregoing methods, the invention includes the further administration of an antiproliferative agent. The compound (e.g., of formula (I), an antihelminthic agent, or otherwise listed above) and antiproliferative agent are administered simultaneously or within 14 days of each other, in amounts that together that are effective to inhibit growth of the neoplasm. Optionally, one or more additional antiproliferative agents in addition to the combination above can be administered such that the combination and the antiproliferative agent(s) are administered simultaneously or within 14 days of each other and in amounts that together are effective to inhibit growth of the neoplasm.

The combination of agents can be administered either by the same or different routes of administration. Desirable routes of administration include intravenous, intramuscular, subcutaneous, rectal, oral, topical, intravaginal, and ophthalmic administration.

The compound (e.g., of formula (I), an antihelminthic agent, or otherwise listed above) is administered in an amount, frequency, and duration that measurably inhibits the growth of the neoplasm. Desirably, the compound is administered in an amount between 0.01 and 3000 mg/day, more preferably, in an amount between 0.1 and 2000 mg/day. Alternatively, the compound can be administered as a 0.5% to 25% topical formulation.

By an "antiproliferative agent" is meant a compound that, individually, inhibits the growth of a neoplasm. Antiproliferative agents of the invention include alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF alpha agonists and antagonists, endothelin A receptor antagonists, retinoic acid receptor agonists, immunomodulators, hormonal and antihormonal agents, photodynamic agents, and tyrosine kinase inhibitors. For treating a neoplasm, antiproliferative agents that can be administered in combination with a compound having any of formulas I-V, antihelminthics, or other compounds recited above include one or more of the agents listed in Table 1.

Table 1.

A

Alkylating agents	cyclophosphamide	lomustine
	busulfan	procarbazine
	ifosfamide	altretamine
	melphalan	estramustine phosphate
	hexamethylmelamine	mechlorethamine
	thiotepa	streptozocin
	chlorambucil	temozolomide
	dacarbazine	semustine
	carmustine	
Platinum agents	cisplatin	carboplatinum
	oxaliplatin	ZD-0473 (AnorMED)
	spiroplatinum,	lobaplatin (Aeterna)
	carboxyphthalatoplatinum,	satraplatin (Johnson Matthey)
	tetraplatin	BBR-3464 (Hoffmann-La Roche)
	ormiplatin	SM-11355 (Sumitomo)
	iproplatin	AP-5280 (Access)
Antimetabolites	azacytidine	tomudex
	gemcitabine	trimetrexate
	capecitabine	deoxycoformycin
	5-fluorouracil	fludarabine
	floxuridine	pentostatin
	2-chlorodeoxyadenosine	raltitrexed
	6-mercaptopurine	hydroxyurea
	6-thioguanine	decitabine (SuperGen)
	cytarabin	clofarabine (Bioenvision)
	2-fluorodeoxy cytidine	irofulven (MGI Pharma)
	methotrexate	DMDC (Hoffmann-La Roche)
	idatrexate	ethynylcytidine (Taiho)
Topoisomerase inhibitors	amsacrine	rubitecan (SuperGen)
	epirubicin	exatecan mesylate (Daiichi)
	etoposide	quinamed (ChemGenex)
	teniposide or mitoxantrone	gimatecan (Sigma-Tau)
	irinotecan (CPT-11)	diflomotecan (Beaufour-Ipsen)
	7-ethyl-10-hydroxy-camptothecin	TAS-103 (Taiho)
	topotecan	elsamitrucin (Spectrum)
	dexrazoxanet (TopoTarget)	J-107088 (Merck & Co)
	pixantrone (Novuspharma)	BNP-1350 (BioNumerik)
	rebeccamycin analogue (Exelixis)	CKD-602 (Chong Kun Dang)
	BBR-3576 (Novuspharma)	KW-2170 (Kyowa Hakko)
Antitumor antibiotics	dactinomycin (actinomycin D)	amonafide
	doxorubicin (adriamycin)	azonafide
	deoxyrubicin	anthrapyrazole
	valrubicin	oxantrazole
	daunorubicin (daunomycin)	losoxantrone
	epirubicin	bleomycin sulfate (blenoxane)
	therarubicin	bleomycinic acid
	idarubicin	bleomycin A
	rubidazone	bleomycin B
	plicamycinp	mitomycin C
	porfiromycin	MEN-10755 (Menarini)
	cyanomorpholinodoxorubicin	GPX-100 (Gem Pharmaceuticals)
	mitoxantrone (novantrone)	

Antimitotic agents	paclitaxel	SB 408075 (GlaxoSmithKline)
	docetaxel	E7010 (Abbott)
	colchicine	PG-TXL (Cell Therapeutics)
	vinblastine	IDN 5109 (Bayer)
	vincristine	A 105972 (Abbott)
	vinorelbine	A 204197 (Abbott)
	vindesine	LU 223651 (BASF)
	dolastatin 10 (NCI)	D 24851 (ASTAMedica)
	rhizoxin (Fujisawa)	ER-86526 (Eisai)
	mivobulin (Warner-Lambert)	combretastatin A4 (BMS)
	cemadotin (BASF)	isohomohalichondrin-B (PharmaMar)
	RPR 109881A (Aventis)	ZD 6126 (AstraZeneca)
	TXD 258 (Aventis)	PEG-paclitaxel (Enzon)
	epothilone B (Novartis)	AZ10992 (Asahi)
	T 900607 (Tularik)	IDN-5109 (Indena)
	T 138067 (Tularik)	AVLB (Prescient NeuroPharma)
	cryptophycin 52 (Eli Lilly)	azaepothilone B (BMS)
	vinflunine (Fabre)	BNP-7787 (BioNumerik)
	auristatin PE (Teikoku Hormone)	CA-4 prodrug (OXiGENE)
	BMS 247550 (BMS)	dolastatin-10 (NIH)
	BMS 184476 (BMS)	CA-4 (OXiGENE)
	BMS 188797 (BMS)	
	taxoprexin (Protarga)	
Aromatase inhibitors	aminoglutethimide	exemestane
	letrozole	atamestane (BioMedicines)
	anastrazole	YM-511 (Yamanouchi)
	formestane	
Thymidylate synthase inhibitors	pemetrexed (Eli Lilly)	nolatrexed (Eximias)
	ZD-9331 (BTG)	CoFactor™ (BioKeys)
DNA antagonists	trabectedin (PharmaMar)	mafosfamide (Baxter International)
	glufosfamide (Baxter International)	apaziquone (Spectrum Pharmaceuticals)
	albumin + 32P (Isotope Solutions)	O6 benzyl guanine (Paligent)
	thymectacin (NewBiotics)	
	edotreotide (Novartis)	
Farnesyltransferase inhibitors	arglabin (NuOncology Labs)	tipifarnib (Johnson & Johnson)
	lonafarnib (Schering-Plough)	perillyl alcohol (DOR BioPharma)
	BAY-43-9006 (Bayer)	
Pump inhibitors	CBT-1 (CBA Pharma)	zosuquidar trihydrochloride (Eli Lilly)
	tariquidar (Xenova)	biricodar dicitrate (Vertex)
	MS-209 (Schering AG)	
Histone acetyltransferase inhibitors	tacedinaline (Pfizer)	pivaloyloxymethyl butyrate (Titan)
	SAHA (Aton Pharma)	depsipeptide (Fujisawa)
	MS-275 (Schering AG)	
Metalloproteinase inhibitors	Neovastat (Aeterna Laboratories)	CMT-3 (CollaGenex)
	marimastat (British Biotech)	BMS-275291 (Celltech)
Ribonucleoside reductase inhibitors	gallium maltolate (Titan)	tezacitabine (Aventis)
	triapine (Vion)	didox (Molecules for Health)
TNF alpha agonists/antagonists	virulizin (Lorus Therapeutics)	revimid (Celgene)
	CDC-394 (Celgene)	

Endothelin A receptor antagonist	atrasentan (Abbott) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
Retinoic acid receptor agonists	fenretinide (Johnson & Johnson) LGD-1550 (Ligand)	alitretinoin (Ligand)
Immuno-modulators	interferon oncophage (Antigenics) GMK (Progenics) adenocarcinoma vaccine (Biomira) CTP-37 (AVI BioPharma) IRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech) synchrovax vaccines (CTL Immuno) melanoma vaccine (CTL Immuno) p21 RAS vaccine (GemVax)	dexosome therapy (Anosys) pentrix (Australian Cancer Technology) ISF-154 (Tragen) cancer vaccine (Intercell) norelin (Biostar) BLP-25 (Biomira) MGV (Progenics) ß-alethine (Dovetail) CLL therapy (Vasogen)
Hormonal and antihormonal agents	estrogens conjugated estrogens ethinyl estradiol chlortrianisen idenestrol hydroxyprogesterone caproate medroxyprogesterone testosterone testosterone propionate; fluoxymesterone methyltestosterone diethylstilbestrol megestrol tamoxifen toremofine dexamethasone	prednisone methylprednisolone prednisolone aminoglutethimide leuprolide goserelin leuporelin bicalutamide flutamide octreotide nilutamide mitotane P-04 (Novogen) 2-methoxyestradiol (EntreMed) arzoxifene (Eli Lilly)
Photodynamic agents	talaporfin (Light Sciences) Theralux (Theratechnologies) motexafin gadolinium (Pharmacyclics)	Pd-bacteriopheophorbide (Yeda) lutetium texaphyrin (Pharmacyclics) hypericin
Tyrosine Kinase Inhibitors	imatinib (Novartis) leflunomide (Sugen/Pharmacia) ZD1839 (AstraZeneca) erlotinib (Oncogene Science) canertinib (Pfizer) squalamine (Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) vatalanib (Novartis) PKI166 (Novartis) GW2016 (GlaxoSmithKline) EKB-509 (Wyeth) EKB-569 (Wyeth)	kahalide F (PharmaMar) CEP-701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) phenoxodiol (Novogen) trastuzumab (Genentech) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone)

E
Miscellaneous agents

SR-27897 (CCK A inhibitor, Sanofi-Synthelabo)
tocladesine (cyclic AMP agonist, Ribapharm)
alvocidib (CDK inhibitor, Aventis)
CV-247 (COX-2 inhibitor, Ivy Medical)
P54 (COX-2 inhibitor, Phytopharm)
CapCell™ (CYP450 stimulant, Bavarian Nordic)
GCS-100 (gal3 antagonist, GlycoGenesys)
G17DT immunogen (gastrin inhibitor, Aphton)
efaproxiral (oxygenator, Allos Therapeutics)
PI-88 (heparanase inhibitor, Progen)
tesmilifene (histamine antagonist, YM BioSciences)
histamine (histamine H2 receptor agonist, Maxim)
tiazofurin (IMPDH inhibitor, Ribapharm)
cilengitide (integrin antagonist, Merck KGaA)
SR-31747 (IL-1 antagonist, Sanofi-Synthelabo)
CCI-779 (mTOR kinase inhibitor, Wyeth)
exisulind (PDE V inhibitor, Cell Pathways)
CP-461 (PDE V inhibitor, Cell Pathways)
AG-2037 (GART inhibitor, Pfizer)
WX-UK1 (plasminogen activator inhibitor, Wilex)
PBI-1402 (PMN stimulant, ProMetic LifeSciences)
bortezomib (proteasome inhibitor, Millennium)
SRL-172 (T cell stimulant, SR Pharma)
TLK-286 (glutathione S transferase inhibitor, Telik)
PT-100 (growth factor agonist, Point Therapeutics)
midostaurin (PKC inhibitor, Novartis)
bryostatin-1 (PKC stimulant, GPC Biotech)
CDA-II (apoptosis promotor, Everlife)
SDX-101 (apoptosis promotor, Salmedix)
ceflatonin (apoptosis promotor, ChemGenex)
BCX-1777 (PNP inhibitor, BioCryst)
ranpirnase (ribonuclease stimulant, Alfacell)
galarubicin (RNA synthesis inhibitor, Dong-A)
tirapazamine (reducing agent, SRI International)
N-acetylcysteine (reducing agent, Zambon)
R-flurbiprofen (NF-kappaB inhibitor, Encore)
3CPA (NF-kappaB inhibitor, Active Biotech)
seocalcitol (vitamin D receptor agonist, Leo)
131-I-TM-601 (DNA antagonist, TransMolecular)
eflornithine (ODC inhibitor, ILEX Oncology)
minodronic acid (osteoclast inhibitor, Yamanouchi)
indisulam (p53 stimulant, Eisai)
aplidine (PPT inhibitor, PharmaMar)
rituximab (CD20 antibody, Genentech)
gemtuzumab (CD33 antibody, Wyeth Ayerst)
PG2 (hematopoiesis enhancer, Pharmagenesis)
Immunol™ (triclosan oral rinse, Endo)
triacetyluridine (uridine prodrug, Wellstat)
SN-4071 (sarcoma agent, Signature BioScience)
TransMID-107™ (immunotoxin, KS Biomedix)
PCK-3145 (apoptosis promotor, Procyon)
doranidazole (apoptosis promotor, Pola)
CHS-828 (cytotoxic agent, Leo)
trans-retinoic acid (differentiator, NIH)
MX6 (apoptosis promotor, MAXIA)
apomine (apoptosis promotor, ILEX Oncology)
urocidin (apoptosis promotor, Bioniche)
Ro-31-7453 (apoptosis promotor, La Roche)
brostallicin (apoptosis promotor, Pharmacia)

Furthermore, the invention also features a composition that includes (i) a compound described above (e.g., of formula (I), an antihelminthic agent, or otherwise listed above) and (ii) an antiproliferative agent.

The invention also features a method for identifying combinations of compounds useful for treating a patient having a neoplasm. The method includes the steps of (a) contacting cancer cells *in vitro* with (i) niclosamide or an antiproliferative agent and (ii) a candidate compound, and (b) determining whether the combination of niclosamide or an antiproliferative and the candidate compound reduces growth of the cancer cells relative to cancer cells contacted with niclosamide or an antiproliferative agent but not contacted with the candidate compound, or cancer cells contacted with the candidate compound but

not with niclosamide or an antiproliferative agent. A reduction of cell growth identifies a combination that is useful for treating a patient having a neoplasm.

Therapy may be provided wherever cancer therapy is performed: at home, the doctor's office, a clinic, a hospital's outpatient department, or a hospital. Treatment generally begins at a hospital so that the doctor can observe the therapy's effects closely and make any adjustments that are needed. The duration of the therapy depends on the kind of cancer being treated, the age and condition of the patient, the stage and type of the patient's disease, and how the patient's body responds to the treatment. Drug administration may be performed at different intervals (e.g., daily, weekly, or monthly). Therapy may be given in on-and-off cycles that include rest periods so that the patient's body has a chance to build healthy new cells and regain its strength.

Depending on the type of cancer and its stage of development, the therapy can be used to slow the spreading of the cancer, to slow the cancer's growth, to kill or arrest cancer cells that may have spread to other parts of the body from the original tumor, to relieve symptoms caused by the cancer, or to prevent cancer in the first place. Cancers that can be treated using the methods of the invention include, without limitation, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, polycythemia vera, Hodgkin's disease, non-Hodgkin's disease, Waldenstrom's macroglobulinemia, heavy chain disease, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct

carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodenroglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

The administration of a combination of the present invention, for the treatment of neoplasms, allows for the administration of lower doses of each compound, providing similar efficacy and lower toxicity compared to administration of either compound alone. Alternatively, such combinations result in improved efficacy in treating neoplasms with similar or reduced toxicity.

As used herein, the terms "cancer" or "neoplasm" or "neoplastic cells" is meant a collection of cells multiplying in an abnormal manner. Cancer growth is uncontrolled and progressive, and occurs under conditions that would not elicit, or would cause cessation of, multiplication of normal cells.

By "inhibits the growth of a neoplasm" is meant measurably slows, stops, or reverses the growth rate of the neoplasm or neoplastic cells *in vitro* or *in vivo*. Desirably, a slowing of the growth rate is by at least 20%, 30%, 50%, or even 70%, as determined using a suitable assay for determination of cell growth rates (e.g., a cell growth assay described herein). Typically, a reversal of growth rate is accomplished by initiating or accelerating necrotic or apoptotic mechanisms of cell death in the neoplastic cells, resulting in a shrinkage of the neoplasm.

By "an effective amount" is meant the amount of a compound required to inhibit the growth of the cells of a neoplasm. The effective amount of active compound(s) used to practice the present invention for therapeutic treatment of neoplasms (i.e., cancer) varies depending upon the manner of administration, the age, body weight, and general health of the subject. Ultimately, the attending physician or veterinarian will decide the appropriate amount and dosage regimen. Such amount is referred to as an "effective" amount.

By "patient" is meant any mammal. Patients include, without limitation, humans, primates, dogs, cats, horses, goats, sheep, cows, pigs, rabbits, and mice.

In the generic descriptions of compounds of this invention, the number of atoms of a particular type in a substituent group is generally given as a range, e.g., an alkyl group containing from 1 to 7 carbon atoms or C_{1-7} alkyl. Reference to such a range is intended to include specific references to groups having each of the integer number of atoms within the specified range. For example, an alkyl group from 1 to 7 carbon atoms includes each of C_1, C_2, C_3, C_4, C_5, C_6, and C_7. A C_{1-7} heteroalkyl, for example, includes from 1 to 6 carbon atoms in addition to one or more heteroatoms. Other numbers of atoms and other types of atoms may be indicated in a similar manner.

As used herein, the terms "alkyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e., cycloalkyl. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 6 ring carbon atoms, inclusive. Exemplary cyclic groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups. The C_{1-7} alkyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{1-7} alkyls include, without limitation, methyl; ethyl; n-propyl; isopropyl; cyclopropyl; cyclopropylmethyl; cyclopropylethyl; n-butyl; iso-butyl; sec-butyl; tert-butyl; cyclobutyl; cyclobutylmethyl; cyclobutylethyl; n-pentyl; cyclopentyl; cyclopentylmethyl; cyclopentylethyl; 1-methylbutyl; 2-methylbutyl; 3-methylbutyl; 2,2-dimethylpropyl; 1-ethylpropyl; 1,1-dimethylpropyl; 1,2-dimethylpropyl; 1-methylpentyl; 2-methylpentyl; 3-methylpentyl; 4-methylpentyl; 1,1-dimethylbutyl; 1,2-dimethylbutyl; 1,3-dimethylbutyl; 2,2-dimethylbutyl; 2,3-dimethylbutyl; 3,3-dimethylbutyl; 1-ethylbutyl; 2-ethylbutyl; 1,1,2-trimethylpropyl; 1,2,2-trimethylpropyl; 1-ethyl-1-methylpropyl; 1-ethyl-2-methylpropyl; and cyclohexyl.

By "C_{2-7} alkenyl" is meant a branched or unbranched hydrocarbon group containing one or more double bonds and having from 2 to 7 carbon atoms. A C_{2-7} alkenyl may optionally include monocyclic or polycyclic rings, in which each

ring desirably has from three to six members. The C_{2-7} alkenyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{2-7} alkenyls include, without limitation, vinyl; allyl; 2-cyclopropyl-1-ethenyl; 1-propenyl; 1-butenyl; 2-butenyl; 3-butenyl; 2-methyl-1-propenyl; 2-methyl-2-propenyl; 1-pentenyl; 2-pentenyl; 3-pentenyl; 4-pentenyl; 3-methyl-1-butenyl; 3-methyl-2-butenyl; 3-methyl-3-butenyl; 2-methyl-1-butenyl; 2-methyl-2-butenyl; 2-methyl-3-butenyl; 2-ethyl-2-propenyl; 1-methyl-1-butenyl; 1-methyl-2-butenyl; 1-methyl-3-butenyl; 2-methyl-2-pentenyl; 3-methyl-2-pentenyl; 4-methyl-2-pentenyl; 2-methyl-3-pentenyl; 3-methyl-3-pentenyl; 4-methyl-3-pentenyl; 2-methyl-4-pentenyl; 3-methyl-4-pentenyl; 1,2-dimethyl-1-propenyl; 1,2-dimethyl-1-butenyl; 1,3-dimethyl-1-butenyl; 1,2-dimethyl-2-butenyl; 1,1-dimethyl-2-butenyl; 2,3-dimethyl-2-butenyl; 2,3-dimethyl-3-butenyl; 1,3-dimethyl-3-butenyl; 1,1-dimethyl-3-butenyl and 2,2-dimethyl-3-butenyl.

By "C_{2-7} alkynyl" is meant a branched or unbranched hydrocarbon group containing one or more triple bonds and having from 2 to 7 carbon atoms. A C_{2-7} alkynyl may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has five or six members. The C_{2-7} alkynyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxy, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{2-7} alkynyls include, without limitation, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 5-hexene-1-ynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl; 1-methyl-2-propynyl; 1-methyl-2-butynyl; 1-methyl-3-butynyl; 2-methyl-3-butynyl; 1,2-dimethyl-3-butynyl; 2,2-dimethyl-3-butynyl; 1-methyl-2-pentynyl; 2-methyl-3-pentynyl; 1-methyl-4-pentynyl; 2-methyl-4-pentynyl; and 3-methyl-4-pentynyl.

By "C_{2-6} heterocyclyl" is meant a stable 5- to 7-membered monocyclic or 7- to 14-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of 2 to 6 carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O, and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxy, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be covalently attached via any heteroatom or carbon atom which results in a stable structure, e.g., an imidazolinyl ring may be linked at either of the ring-carbon atom positions or at the nitrogen atom. A nitrogen atom in the heterocycle may optionally be quaternized. Preferably when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. Heterocycles include, without limitation, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl,

pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred 5 to 10 membered heterocycles include, but are not limited to, pyridinyl, pyrimidinyl, triazinyl, furanyl, thienyl, thiazolyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, tetrazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolidinyl, isoxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, quinolinyl, and isoquinolinyl. Preferred 5 to 6 membered heterocycles include, without limitation, pyridinyl, pyrimidinyl, triazinyl, furanyl, thienyl, thiazolyl, pyrrolyl, piperazinyl, piperidinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, and tetrazolyl.

By "C_{6-12} aryl" is meant an aromatic group having a ring system comprised of carbon atoms with conjugated π electrons (e.g., phenyl). The aryl group has from 6 to 12 carbon atoms. Aryl groups may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has five or six members. The aryl group may be substituted or unsubstituted. Exemplary subsituents include alkyl, hydroxy, alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, fluoroalkyl, carboxyl, hydroxyalkyl, carboxyalkyl, amino, aminoalkyl, monosubstituted amino, disubstituted amino, and quaternary amino groups.

By "C_{7-14} alkaryl" is meant an alkyl substituted by an aryl group (e.g., benzyl, phenethyl, or 3,4-dichlorophenethyl) having from 7 to 14 carbon atoms.

By "C_{3-10} alkheterocyclyl" is meant an alkyl substituted heterocyclic group having from 3 to 10 carbon atoms in addition to one or more heteroatoms (e.g., 3-furanylmethyl, 2-furanylmethyl, 3-tetrahydrofuranylmethyl, or 2-tetrahydrofuranylmethyl).

By "C_{1-7} heteroalkyl" is meant a branched or unbranched alkyl, alkenyl, or alkynyl group having from 1 to 7 carbon atoms in addition to one or more heteroatoms, wherein one or more methylenes (CH_2) or methines (CH) are replaced by nitrogen, oxygen, sulfur, carbonyl, thiocarbonyl, phosphoryl, or sulfonyl. Heteroalkyls include, without limitation, tertiary amines, secondary amines, ethers, thioethers, amides, thioamides, carbamates, thiocarbamates, phosphoramidates, sulfonamides, and disulfides. A heteroalkyl may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has three to six members. The heteroalkyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, hydroxyalkyl, carboxyalkyl, and carboxyl groups.

By "acyl" is meant a chemical moiety with the formula R-C(O)-, wherein R is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

By "halide" is meant bromine, chlorine, iodine, or fluorine.

By "fluoroalkyl" is meant an alkyl group that is substituted with a fluorine.

By "perfluoroalkyl" is meant an alkyl group consisting of only carbon and fluorine atoms.

By "carboxyalkyl" is meant a chemical moiety with the formula -(R)-COOH, wherein R is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl..

By "hydroxyalkyl" is meant a chemical moiety with the formula -(R)-OH, wherein R is is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

By "alkoxy" is meant a chemical substituent of the formula -OR, wherein R is is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

By "aryloxy" is meant a chemical substituent of the formula -OR, wherein R is a C_{6-12} aryl group.

By "alkylthio" is meant a chemical substituent of the formula -SR, wherein R is is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

By "arylthio" is meant a chemical substituent of the formula -SR, wherein R is a C_{6-12} aryl group.

By "quaternary amino" is meant a chemical substituent of the formula -(R)-N(R')(R'')(R''')$^+$, wherein R, R', R'', and R''' are each independently an alkyl, alkenyl, alkynyl, or aryl group. R may be an alkyl group linking the quaternary amino nitrogen atom, as a substituent, to another moiety. The nitrogen atom, N, is covalently attached to four carbon atoms of alkyl and/or aryl groups, resulting in a positive charge at the nitrogen atom.

By an "antihelminthic agent" is meant a compound that, individually, inhibits the growth of a parasitic worm. Desirably, growth rate is reduced by at least 20%, 30%, 50%, or even 70%. Examples of helminthes include cestodes, trematodes, nematodes, *Fasciola*, *Schistosoma*, planaria, filaria, and *Trichinella*. Antihelminthic agents encompass a broad spectrum of modes of action which include: glutamate-gated chloride channel potentiating compounds such as ivermectin, abamectin, doramectin, moxidectin, niclofolan, and mylbemycin D; calcium permeability potentiators such as praziquantel, malate metabolism inhibitors such as diamphenethide; phosphoglycerate kinase and mutase inhibitors such as chlorsulon; and salicylanilide compounds. Preferred antihelminthic agents are the salicylanilides, which consist of a salicylic acid ring and an anilide ring. Examples of antihelminthic salicylanilides include niclosamide, oxyclozanide, closantel, rafoxanide, resorantel, clioxanide, tribromsalan, dibromsalan, and brotianide.

Compounds useful in the invention include those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, and polymorphs, thereof, as well as racemic mixtures of the compounds described herein.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

Brief Description of the Drawing

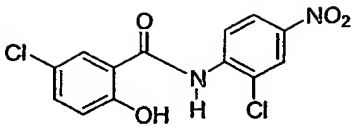
Fig. 1 is a schematic illustration showing the antiproliferative activity of niclosamide against several cancer cell lines *in vitro*.

Detailed Description

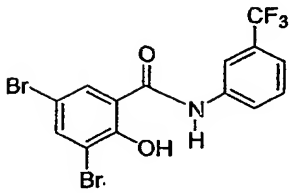
We have discovered that the salicylanilide compound niclosamide exhibits antiproliferative activity against cancer cells and enhances the antiproliferative activity of known antiproliferative agents against cancer cells *in vitro*. Thus, niclosamide and structural and functional analogs of niclosamide are useful as antiproliferative agents for the treatment of cancer and other neoplasms either administered alone or in combination with known antiproliferative agents.

Niclosamide

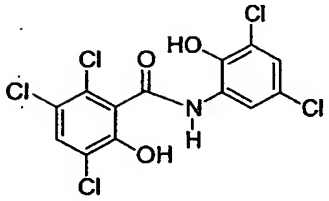
Niclosamide (2',5-dichloro-4'-nitrosalicylanilide) is an antihelminthic used for treatment of cestode and trematode infestations in humans, pets, and, livestock. This drug has also been used as an effective lampricide and a pesticide against fresh water snails. The free base, the monohydrate, the ethanolamine salt, and the piperazine salt are know to be active as antihelmenthic agents. The structure of niclosamide and other benzanilide antihelmenthic agents are provided below.



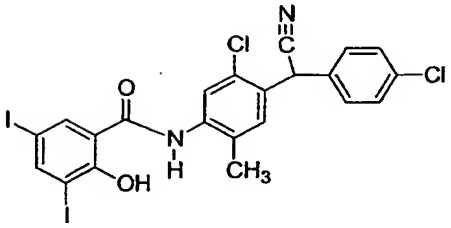
niclosamide



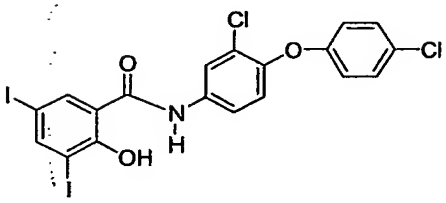
flusalan



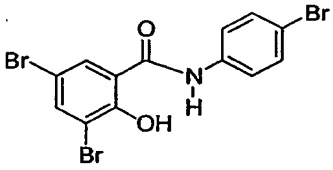
oxyclozanide



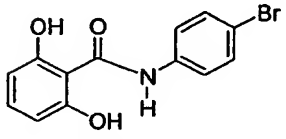
closantel



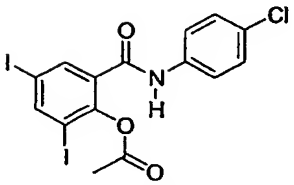
rafoxanide



tribromsalan



resorantel



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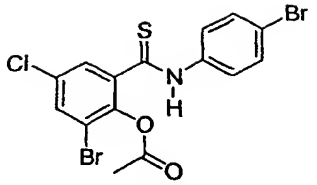
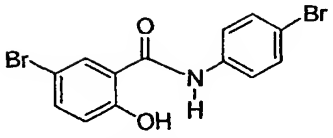


brotianide

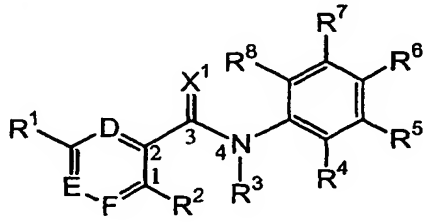


dibromsalan

Niclosamide exhibits very low toxicity in mammals. Studies on rats have shown oral administration of niclosamide to have an LD_{50} of 5000 mg/kg (body weight). The LD_{50} of the ethanolamine, piperazine, and monohydrate salts are 10000, 5000, and 5000 mg/kg body weight, respectively in rats. Further toxicological studies on the ethanolamine salt on rats have shown niclosamide to have an LD_{50} of 2000 mg/kg (body weight) for dermal applications, 44-250 mg/kg (body weight) for intraperitoneal injection, 7 mg/kg (body weight) for intravenous injection, and 2270 $mg/m^3/hr$ when inhaled. No toxic or detrimental effects were observed when rats were fed moderate to high doses of niclosamide for over one year. Furthermore, there are no known carcinogenic, mutagenic, or teratogenic effects associated with niclosamide administration.

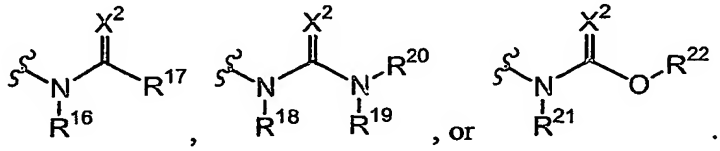
Benzanilides

Salicylanilides such as niclosamide consist of a salicylic acid ring and an anilide ring. Salicylanilides are a subset of benzanilides; benzanilides that can be used according to the methods of the invention include those that fit formula I:

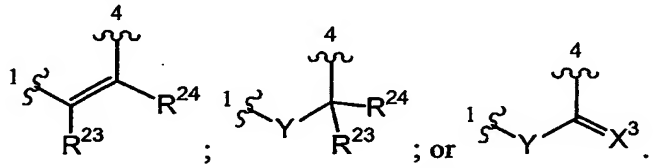


I

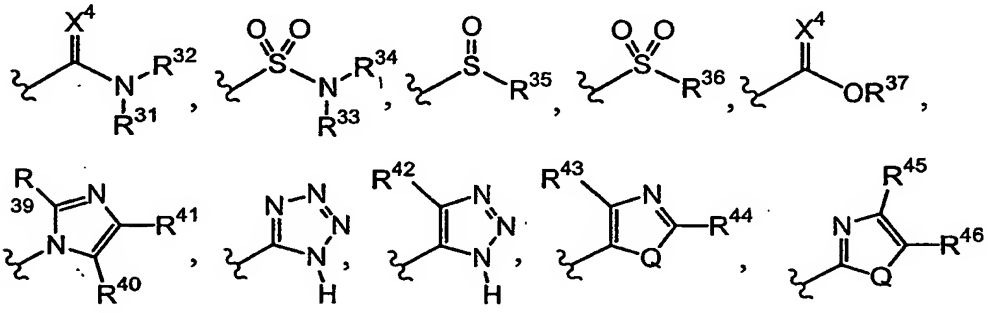
or a salt thereof. In formula I D is N or CR^9; E is N or CR^{10}; F is N or CR^{11}; and R^1 is H, halide, OR^{12}, SR^{13}, $NR^{14}R^{15}$, or described by one of the formulas:



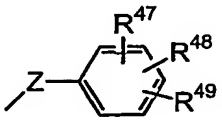
R^2 is H, OH, or OR^{12}; R^3 is H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; or R^2 and R^3 combine to form a six-membered ring in which position 1 is connected to position 4 by one of the groups:



R^4 and R^8 are each, independently, selected from H, halide, CF_3, OR^{28}, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; and R^5, R^6, and R^7 are each, independently, selected from H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl, halide, NO_2, CO_2H, SO_3H, CF_3, CN, OR^{29}, SR^{30}, or are described by the formulas:



or

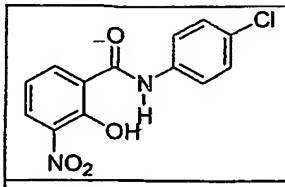
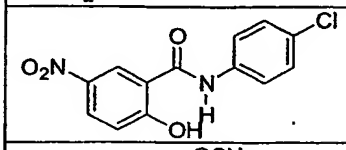
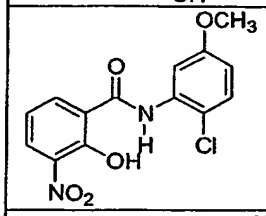
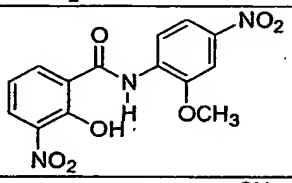
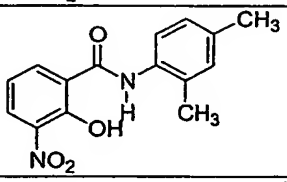
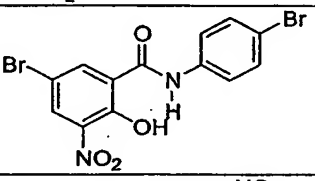
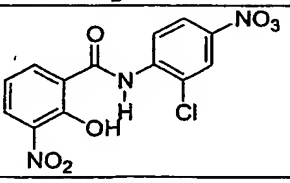
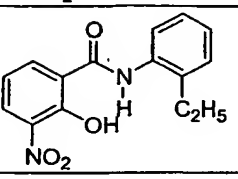


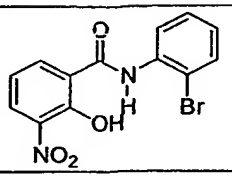
For compounds of formula I, each X^1, X^2, X^3, and X^4 is, independently, O S; or NR^{38}; Y is $CR^{25}R^{26}$, O, S, or NR^{27}; Z is O, S, or $CR^{50}R^{51}$; each Q is, independently, O, S, or NR^{52}; R^9, R^{10}, and R^{11} are each, independently, H, OH, OR^{12}, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-7} heteroalkyl, halide, or NO_2; R^{12} and R^{13} are each, independently, acyl, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; R^{17}, R^{22}, R^{35}, R^{36}, R^{37}, R^{38}, and R^{52} are each, independently, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; R^{14}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, and R^{47} are each, independently, H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; and R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, and R^{51} are each, independently, H, halide, CN, NO_2, CF_3, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

Benzanilides that can be used according to the methods of the invention include niclosamide, oxyclozanide, closantel, resorantel, tribromsalan, clioxanide, dibromsalan, rafoxanide, flusalan, and the compounds disclosed in U.S. Patent Nos. 3,041,236, 3,079,297, 3,113,067, 3,147,300, 3,332,996, 3,349,090, 3,449,420, 3,466,370, 3,469,006, 3,499,420, 3,798,258, 3,823,236, 3,839,443, 3,888,980, 3,906,023, 3,927,071, 3,949,075, 3,973,038, 4,005,218, 4,008,274, 4,072,753, 4,115,582, 4,159,342, 4,310,682, and 4,470,979, each of which is hereby incorporated by reference, Hlasta et al., Bioorg. Med. Chem., and European Patent No. 0533268. Salts or esters of any of these compounds can also be used according to the methods of the invention.

Salicylanilides are particularly desirable compounds for use in the methods of the invention. Exemplary salicylanilide compounds that can be used according to the methods of invention are depicted in Table 2.

Table 2

	4'-chloro-3-nitrosalicylanilide
	4'-chloro-5-nitrosalicylanilide
	2'-chloro-5'-methoxy-3-nitrosalicylanilide
	2'-methoxy-3,4'-dinitrosalicylanilide
	2',4'-dimethyl-3-nitrosalicylanilide
	4',5-dibromo-3-nitrosalicylanilide
	2'-chloro-3,4'-dinitrosalicylanilide
	2'-ethyl-3-nitrosalicylanilide

	2'-bromo-3-nitrosalicylanilide

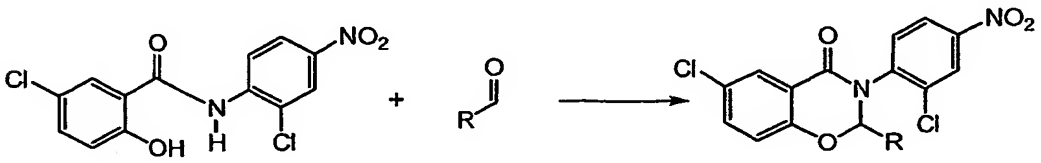
Functional Analogs of Niclosamide

Based on the shared antihelmenthic activity, compounds such as ivermectin, abamectin, doramectin, moxidectin, mylbemycin D, niclofolan, praziquantel, diamphenethide, and chlorsulon can be substituted for niclosamide in the methods of the invention. Other antihelmenthic agents are known in the art; these compounds can also be employed in the methods of the invention.

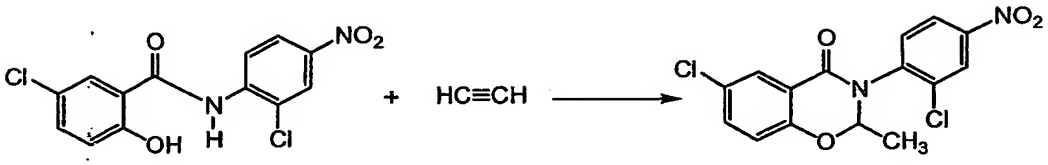
Synthetic Methods

Methods for synthesizing benzanilide and salicylanilide derivatives are well known in the art. For example, niclosamide and related compounds can be prepared as described in U.S. Patent Nos. 3,079,297 and 3,113,067; flusalan and related compounds can be prepared as described in U.S. Patent No. 3,041,236; oxyclozanide and related compounds can be prepared as described in U.S. Patent No. 3,349,090; closantel and related compounds can be prepared as described in U.S. Patent No. 4,005,218; resorantel and related compounds can be prepared as described in U.S. Patent No. 3,449,420; tribromsalan, dibromsalan, and related compounds can be prepared as described in U.S. Patent Nos. 2,967,885 and 3,064,048; clioxanide and related compounds can be prepared as described by Campbell et al., *Experientia* 23:992 (1967); and rafoxanide and related compounds can be prepared as described by Mrozak et al., *Experientia* 25:883 (1969). Additional methods are disclosed by, for example, Hlasta et al., *Bioorg. Med. Chem.*, U.S. Patent Nos. 3,466,370, 3,888,980, 3,973,038, 4,008,274, 4,072,753, and 4,115,582, and European Patent No. 0533268. All publications and patents mentioned above are incorporated herein by reference.

Compounds of formula IV can be prepared, for example, by condensation of a salicylanilide with an aldehyde, see reaction 1, as described in *Acta Pharmaceutica (Zagreb)* 50:239 (2000); or by reaction with acetylene, see reaction 2, as described in *Khimiya Geterotsiklicheskikh Soedinenii* 4:469 (1983) or *Khimiya Geterotsiklicheskikh Soedinenii* 9:1278 (1979).

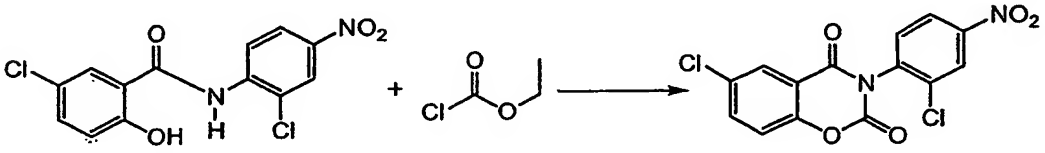


reaction 1



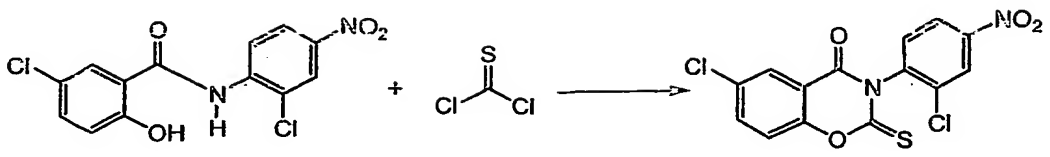
reaction 2

Compounds of formula III in which X^3 is an oxygen atom can be prepared, for example, by condensation of a salicylanilide with ethyl chloroformate, see reaction 3, as described in *Pharmazie* 45:34 (1990); *J. Med. Chem.* 32:807 (1989); or *J. Med. Chem.* 21:1178 (1978).



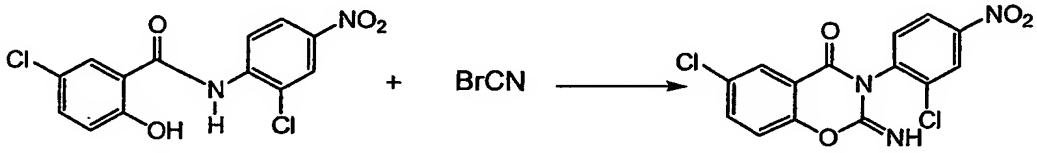
reaction 3

Compounds of formula III in which X^3 is a sulfur atom can be prepared, for example, by condensation of a salicylanilide with thiophosgene, see reaction 4, as described in *Archiv der Pharmazie (Weinheim, Germany)* 315:97 (1982); *Indian J. Chem., Sect. B* 18:352 (1979); *Indian J. Chem., Sect. B* 15:73 (1977); or *Indian J. Pharm.*, 37:133 (1975).



reaction 4

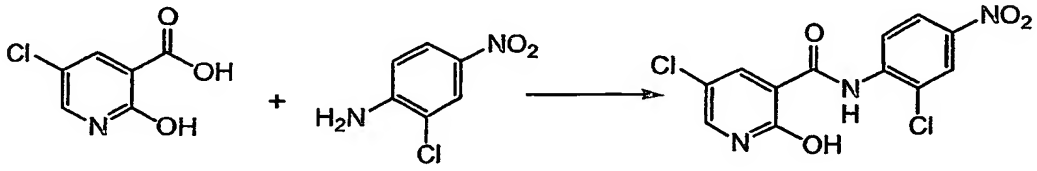
Compounds of formula III in which X^3 is NH can be prepared, for example, by reaction of a salicylanilide with cyanogen bromide, see reaction 5, as described in *C. R. Hebd. Seances Acad. Sci., Ser. C* 283:291 (1976).



reaction 5

Compounds of formula I in which D, E, or F is a nitrogen atom can be prepared using methods analogous to those used for the synthesis of salicylanilide compounds. For example, 2-hydroxynicotinic acid (Aldrich Cat. No. 25,105-4), 3-hydroxypicolinic acid (Aldrich Cat. No. 15,230-7), 6-hydroxynicotinic acid (Aldrich Cat. No. 12,875-9), 6- hydroxypicolinic acid (Aldrich Cat. No. 38,430-5), 5-chloro-6-hydroxynicotinic acid (Fluka Cat. No. 24882), 5-bromonicotinic acid (Aldrich Cat. No. 22843-5), 2-chloronicotinic acid (Aldrich Cat. No. 15,033-9), 6-chloronicotinic acid (Aldrich Cat. No. 15,635-3), 5,6-dichloronicotinic acid (Aldrich Cat. No. 34,021-9), or citrazinic acid (Aldrich Cat. No. 15,328-1) can be reacted with an aniline to produce a compound of formula I in which D, E, or F are a nitrogen atom. Furthermore, 2-hydroxynicotinic acid derivatives and 3-hydroxypyrazine-2-carboxylic acid derivatives can be prepared using the methods described in U.S. Patent Nos. 5,364,940, 5,516,661, and 5,364,939. For example, 5-chloronicotinic acid (CAS 22620-27-5) can be hydroxylated using the methods described in U.S. Patent No. 5,364,940 and the resulting 2-hydroxy-5-

chloronicotinic acid coupled with 2-chloro-4-nitroaniline (Aldrich Cat. No. 45,685-3), as shown in reaction 6, using standard amide coupling techniques.



reaction 6

The resulting product is a compound of formula I and can be used in the methods of the invention

Antiproliferative Agents

Antiproliferative agents that can be administered in the combinations of the invention are alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF alpha agonists and antagonists, endothelin A receptor antagonists, retinoic acid receptor agonists, immunomodulators, hormonal and antihormonal agents, photodynamic agents, and tyrosine kinase inhibitors. Any one or more of the agents listed in Table 1 can be used. Exemplary antiproliferative agents include, without limitation, paclitaxel, gemcitabine, doxorubicin, vinblastine, etoposide, 5-fluorouracil, carboplatin, altretamine, aminoglutethimide, amsacrine, anastrozole, azacitidine, bleomycin, busulfan, carmustine, chlorambucil, 2-chlorodeoxyadenosine, cisplatin, colchicine, cyclophosphamide, cytarabine, cytoxan, dacarbazine, dactinomycin, daunorubicin, docetaxel, estramustine phosphate, floxuridine, fludarabine, gentuzumab, hexamethylmelamine, hydroxyurea, ifosfamide, imatinib, interferon, irinotecan, lomustine, mechlorethamine, melphalen, 6-mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, pentostatin,

procarbazine, rituximab, streptozocin, tamoxifen, temozolomide, teniposide, 6-thioguanine, topotecan, trastuzumab, vincristine, vindesine, and vinorelbine.

Therapy

The methods and compounds of the invention are useful for the treatment of neoplasms. Therapy may be performed alone or in conjunction with another therapy (e.g., surgery, radiation, chemotherapy, biologic therapy). Additionally, a person having a greater risk of developing a neoplasm (e.g., one who is genetically predisposed or one who previously had a neoplasm) may receive prophylactic treatment to inhibit or delay neoplastic formation. The duration of the therapy depends on the type of disease or disorder being treated, the age and condition of the patient, the stage and type of the patient's disease, and how the patient responds to the treatment. Therapy may be given in on-and-off cycles that include rest periods so that the patient's body has a chance to recovery from any as yet unforeseen side-effects.

The dosage, frequency and mode of administration of each component of a combination can be controlled independently. For example, one compound (i.e., niclosamide) may be administered orally once per day, while the second compound (i.e., the antiproliferative agent) may be administered intravenously twice per day. Therapy may be given in on-and-off cycles that include rest periods so that the patient's body has a chance to recovery from any as yet unforeseen side-effects. The compounds may also be formulated together such that one administration delivers both compounds. Accordingly, a compound having any of formulas I-V can be administered simultaneously or within 14 days of administration of one or more antiproliferative agents selected from Table 1 for the treatment of any of the cancers listed above.

Examples of cancers and other neoplasms include, without limitation, leukemias (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia),

polycythemia vera, lymphoma (Hodgkin's disease, non-Hodgkin's disease), Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors such as sarcomas and carcinomas (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodenriglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma).

Formulation of Pharmaceutical Compositions

Pharmaceutical compositions of the invention may be by any suitable means that results in a concentration of the compound that is antiproliferative upon reaching the target region. The compound may be contained in any appropriate amount in any suitable carrier substance, and is generally present in an amount of 1-95% by weight of the total weight of the composition. The composition may be provided in a dosage form that is suitable for the oral, parenteral (e.g., intravenously, intramuscularly), rectal, cutaneous, nasal, vaginal, inhalant, skin (patch), or ocular administration route. Thus, the composition may be in the form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, osmotic delivery devices, suppositories, enemas, injectables, implants, sprays, or aerosols. The pharmaceutical compositions may be

formulated according to conventional pharmaceutical practice (see, e.g., Remington: The Science and Practice of Pharmacy (20th ed.), ed. A.R. Gennaro, Lippincott Williams & Wilkins, 2000 and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York).

Pharmaceutical compositions according to the invention may be formulated to release the active compound substantially immediately upon administration or at any predetermined time or time period after administration. The latter types of compositions are generally known as controlled release formulations, which include (i) formulations that create a substantially constant concentration of the drug within the body over an extended period of time; (ii) formulations that after a predetermined lag time create a substantially constant concentration of the drug within the body over an extended period of time; (iii) formulations that sustain drug action during a predetermined time period by maintaining a relatively, constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active drug substance (sawtooth kinetic pattern); (iv) formulations that localize drug action by, e.g., spatial placement of a controlled release composition adjacent to or in the diseased tissue or organ; and (v) formulations that target drug action by using carriers or chemical derivatives to deliver the drug to a particular target cell type.

Administration of compounds in the form of a controlled release formulation is especially preferred in cases in which the compound has (i) a narrow therapeutic index (i.e., the difference between the plasma concentration leading to harmful side effects or toxic reactions and the plasma concentration leading to a therapeutic effect is small; in general, the therapeutic index, TI, is defined as the ratio of median lethal dose (LD50) to median effective dose (ED50)); (ii) a narrow absorption window in the gastro-intestinal tract; or (iii) a very short biological half-life so that frequent dosing during a day is required in order to sustain the plasma level at a therapeutic level.

Any of a number of strategies can be pursued in order to obtain controlled release in which the rate of release outweighs the rate of metabolism of the compound in question. In one example, controlled release is obtained by appropriate selection of various formulation parameters and ingredients, including, e.g., various types of controlled release compositions and coatings. Thus, the drug is formulated with appropriate excipients into a pharmaceutical composition that, upon administration, releases the drug in a controlled manner. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanoparticles, patches, and liposomes.

Solid Dosage Forms For Oral Use

Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (e.g., sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, or sodium phosphate); granulating and disintegrating agents (e.g., cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid); binding agents (e.g., sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically acceptable excipients can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.

The tablets may be uncoated or they may be coated by known techniques, optionally to delay disintegration and absorption in the gastrointestinal tract and thereby providing a sustained action over a longer period. The coating may be

adapted to release the active drug substance in a predetermined pattern (e.g., in order to achieve a controlled release formulation) or it may be adapted not to release the active drug substance until after passage of the stomach (enteric coating). The coating may be a sugar coating, a film coating (e.g., based on hydroxypropyl methylcellulose, methylcellulose, methyl hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, acrylate copolymers, polyethylene glycols and/or polyvinylpyrrolidone), or an enteric coating (e.g., based on methacrylic acid copolymer, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, and/or ethylcellulose). Furthermore, a time delay material such as, e.g., glyceryl monostearate or glyceryl distearate may be employed.

The solid tablet compositions may include a coating adapted to protect the composition from unwanted chemical changes, (e.g., chemical degradation prior to the release of the active drug substance). The coating may be applied on the solid dosage form in a similar manner as that described in Encyclopedia of Pharmaceutical Technology, supra.

Formulations for oral use may also be presented as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (e.g., potato starch, lactose, microcrystalline cellulose, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders and granulates may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid bed apparatus or a spray drying equipment.

Controlled Release Oral Dosage Forms

Controlled release compositions for oral use may, e.g., be constructed to release the active drug by controlling the dissolution and/or the diffusion of the active drug substance.

Dissolution or diffusion controlled release can be achieved by appropriate coating of a tablet, capsule, pellet, or granulate formulation of compounds, or by incorporating the compound into an appropriate matrix. A controlled release coating may include one or more of the coating substances mentioned above and/or, e.g., shellac, beeswax, glycowax, castor wax, carnauba wax, stearyl alcohol, glyceryl monostearate, glyceryl distearate, glycerol palmitostearate, ethylcellulose, acrylic resins, dl-polylactic acid, cellulose acetate butyrate, polyvinyl chloride, polyvinyl acetate, vinyl pyrrolidone, polyethylene, polymethacrylate, methylmethacrylate, 2-hydroxymethacrylate, methacrylate hydrogels, 1,3 butylene glycol, ethylene glycol methacrylate, and/or polyethylene glycols. In a controlled release matrix formulation, the matrix material may also include, e.g., hydrated metylcellulose, carnauba wax and stearyl alcohol, carbopol 934, silicone, glyceryl tristearate, methyl acrylate-methyl methacrylate, polyvinyl chloride, polyethylene, and/or halogenated fluorocarbon.

A controlled release composition containing one or more of the compounds of the invention may also be in the form of a buoyant tablet or capsule (i.e., a tablet or capsule that, upon oral administration, floats on top of the gastric content for a certain period of time). A buoyant tablet formulation of the compound(s) can be prepared by granulating a mixture of the drug(s) with excipients and 20-75% w/w of hydrocolloids, such as hydroxyethylcellulose, hydroxypropylcellulose, or hydroxypropylmethylcellulose. The obtained granules can then be compressed into tablets. On contact with the gastric juice, the tablet forms a substantially water-impermeable gel barrier around its surface. This gel barrier takes part in maintaining a density of less than one, thereby allowing the tablet to remain buoyant in the gastric juice.

Liquids for Oral Administration

Powders, dispersible powders, or granules suitable for preparation of an aqueous suspension by addition of water are convenient dosage forms for oral administration. Formulation as a suspension provides the active ingredient in a mixture with a dispersing or wetting agent, suspending agent, and one or more

preservatives. Suitable dispersing or wetting agents are, for example, naturally-occurring phosphatides (e.g., lecithin or condensation products of ethylene oxide with a fatty acid, a long chain aliphatic alcohol, or a partial ester derived from fatty acids) and a hexitol or a hexitol anhydride (e.g., polyoxyethylene stearate, polyoxyethylene sorbitol monooleate, polyoxyethylene sorbitan monooleate, and the like). Suitable suspending agents are, for example, sodium carboxymethylcellulose, methylcellulose, sodium alginate, and the like.

Parenteral Compositions

The pharmaceutical composition may also be administered parenterally by injection, infusion or implantation (intravenous, intramuscular, subcutaneous, or the like) in dosage forms, formulations, or via suitable delivery devices or implants containing conventional, non-toxic pharmaceutically acceptable carriers and adjuvants. The formulation and preparation of such compositions are well known to those skilled in the art of pharmaceutical formulation. Formulations can be found in Remington: The Science and Practice of Pharmacy, supra.

Compositions for parenteral use may be provided in unit dosage forms (e.g., in single-dose ampoules), or in vials containing several doses and in which a suitable preservative may be added (see below). The composition may be in form of a solution, a suspension, an emulsion, an infusion device, or a delivery device for implantation, or it may be presented as a dry powder to be reconstituted with water or another suitable vehicle before use. Apart from the active drug(s), the composition may include suitable parenterally acceptable carriers and/or excipients. The active drug(s) may be incorporated into microspheres, microcapsules, nanoparticles, liposomes, or the like for controlled release. Furthermore, the composition may include suspending, solubilizing, stabilizing, pH-adjusting agents, and/or dispersing agents.

As indicated above, the pharmaceutical compositions according to the invention may be in the form suitable for sterile injection. To prepare such a composition, the suitable active drug(s) are dissolved or suspended in a parenterally acceptable liquid vehicle. Among acceptable vehicles and solvents

that may be employed are water, water adjusted to a suitable pH by addition of an appropriate amount of hydrochloric acid, sodium hydroxide or a suitable buffer, 1,3-butanediol, Ringer's solution, and isotonic sodium chloride solution. The aqueous formulation may also contain one or more preservatives (e.g., methyl, ethyl or n-propyl p-hydroxybenzoate). In cases where one of the compounds is only sparingly or slightly soluble in water, a dissolution enhancing or solubilizing agent can be added, or the solvent may include 10-60% w/w of propylene glycol or the like.

Controlled Release Parenteral Compositions

Controlled release parenteral compositions may be in form of aqueous suspensions, microspheres, microcapsules, magnetic microspheres, oil solutions, oil suspensions, or emulsions. Alternatively, the active drug(s) may be incorporated in biocompatible carriers, liposomes, nanoparticles, implants, or infusion devices.

Materials for use in the preparation of microspheres and/or microcapsules are, e.g., biodegradable/bioerodible polymers such as polygalactin, poly-(isobutyl cyanoacrylate), poly(2-hydroxyethyl-L-glutamnine) and, poly(lactic acid).

Biocompatible carriers that may be used when formulating a controlled release parenteral formulation are carbohydrates (e.g., dextrans), proteins (e.g., albumin), lipoproteins, or antibodies.

Materials for use in implants can be non-biodegradable (e.g., polydimethyl siloxane) or biodegradable (e.g., poly(caprolactone), poly(lactic acid), poly(glycolic acid) or poly(ortho esters)).

Rectal Compositions

For rectal application, suitable dosage forms for a composition include suppositories (emulsion or suspension type), and rectal gelatin capsules (solutions or suspensions). In a typical suppository formulation, the active drug(s) are combined with an appropriate pharmaceutically acceptable suppository base such as cocoa butter, esterified fatty acids, glycerinated gelatin, and various water-

soluble or dispersible bases like polyethylene glycols and polyoxyethylene sorbitan fatty acid esters. Various additives, enhancers, or surfactants may be incorporated.

Compositions for Inhalation

For administration by inhalation, typical dosage forms include nasal sprays and aerosols. In a typically nasal formulation, the active ingredient(s) are dissolved or dispersed in a suitable vehicle. The pharmaceutically acceptable vehicles and excipients (as well as other pharmaceutically acceptable materials present in the composition such as diluents, enhancers, flavoring agents, and preservatives) are selected in accordance with conventional pharmaceutical practice in a manner understood by the persons skilled in the art of formulating pharmaceuticals.

Percutaneous and Topical Compositions

The pharmaceutical compositions may also be administered topically on the skin for percutaneous absorption in dosage forms or formulations containing conventionally non-toxic pharmaceutical acceptable carriers and excipients including microspheres and liposomes. The formulations include creams, ointments, lotions, liniments, gels, hydrogels, solutions, suspensions, sticks, sprays, pastes, plasters, and other kinds of transdermal drug delivery systems. The pharmaceutically acceptable carriers or excipients may include emulsifying agents, antioxidants, buffering agents, preservatives, humectants, penetration enhancers, chelating agents, gel-forming agents, ointment bases, perfumes, and skin protective agents.

Examples of emulsifying agents are naturally occurring gums (e.g., gum acacia or gum tragacanth) and naturally occurring phosphatides (e.g., soybean lecithin and sorbitan monooleate derivatives). Examples of antioxidants are butylated hydroxy anisole (BHA), ascorbic acid and derivatives thereof, tocopherol and derivatives thereof, butylated hydroxy anisole, and cysteine. Examples of preservatives are parabens, such as methyl or propyl p-

hydroxybenzoate, and benzalkonium chloride. Examples of humectants are glycerin, propylene glycol, sorbitol, and urea. Examples of penetration enhancers are propylene glycol, DMSO, triethanolamine, N,N-dimethylacetamide, N,N-dimethylformamide, 2-pyrrolidone and derivatives thereof, tetrahydrofurfuryl alcohol, and AZONE™. Examples of chelating agents are sodium EDTA, citric acid, and phosphoric acid. Examples of gel forming agents are CARBOPOL™, cellulose derivatives, bentonite, alginates, gelatin and polyvinylpyrrolidone. Examples of ointment bases are beeswax, paraffin, cetyl palmitate, vegetable oils, sorbitan esters of fatty acids (Span), polyethylene glycols, and condensation products between sorbitan esters of fatty acids and ethylene oxide (e.g., polyoxyethylene sorbitan monooleate (TWEEN™)).

The pharmaceutical compositions described above for topical administration on the skin may also be used in connection with topical administration onto or close to the part of the body that is to be treated. The compositions may be adapted for direct application or for introduction into relevant orifice(s) of the body (e.g., rectal, urethral, vaginal or oral orifices). The composition may be applied by means of special drug delivery devices such as dressings or alternatively plasters, pads, sponges, strips, or other forms of suitable flexible material.

Controlled Release Percutaneous and Topical Compositions

There are several approaches for providing rate control over the release and transdermal permeation of a drug, including: membrane-moderated systems, adhesive diffusion-controlled systems, matrix dispersion-type systems, and microreservoir systems. A controlled release percutaneous and/or topical composition may be obtained by using a suitable mixture of the above-mentioned approaches. In a membrane-moderated system, the active drug is present in a reservoir which is totally encapsulated in a shallow compartment molded from a drug-impermeable laminate, such as a metallic plastic laminate, and a rate-controlling polymeric membrane such as a microporous or a non-porous polymeric membrane (e.g., ethylene-vinyl acetate copolymer). The active

compound is only released through the rate-controlling polymeric membrane. In the drug reservoir, the active drug substance may either be dispersed in a solid polymer matrix or suspended in a viscous liquid medium such as silicone fluid. On the external surface of the polymeric membrane, a thin layer of an adhesive polymer is applied to achieve an intimate contact of the transdermal system with the skin surface. The adhesive polymer is preferably a hypoallergenic polymer that is compatible with the active drug.

In an adhesive diffusion-controlled system, a reservoir of the active drug is formed by directly dispersing the active drug in an adhesive polymer and then spreading the adhesive containing the active drug onto a flat sheet of substantially drug-impermeable metallic plastic backing to form a thin drug reservoir layer.

A matrix dispersion-type system is characterized in that a reservoir of the active drug substance is formed by substantially homogeneously dispersing the active drug substance in a hydrophilic or lipophilic polymer matrix and then molding the drug-containing polymer into a disc with a substantially well-defined surface area and thickness. The adhesive polymer is spread along the circumference to form a strip of adhesive around the disc.

In a microreservoir system, the reservoir of the active substance is formed by first suspending the drug solids in an aqueous solution of water-soluble polymer, and then dispersing the drug suspension in a lipophilic polymer to form a plurality of microscopic spheres of drug reservoirs.

Dosages

The dosage of the claimed compounds depends on several factors, including: the administration method, the neoplasm to be treated, the severity of the neoplasm, whether the neoplasm is to be treated or prevented, and the age, weight, and health of the patient to be treated.

As described above, the compound in question may be administered orally in the form of tablets, capsules, elixirs or syrups, or rectally in the form of suppositories. Parenteral administration of a compound is suitably performed, for example, in the form of saline solutions or with the compound incorporated into

liposomes. In cases where the compound in itself is not sufficiently soluble to be dissolved, a solubilizer such as ethanol can be applied. Below, for illustrative purposes, the dosages for niclosamide are described. One in the art will recognize that if an alternative compound is substituted for niclosamide, the correct dosage can be determined by examining the efficacy of the compound in cell proliferation assays, as well as its toxicity in humans. For topical administration, niclosamide is provided in a 1-250 g/L solution, cream, or gel. For parenteral or enteral administration, niclosamide is dosed at about 0.1-50 mg/kg/day. For oral administration, niclosamide is dosed at about 10-3000 mg/day.

Oral Administration

For oral administration, the dosage of niclosamide is normally about 0.001 mg to 3000 mg per dose administered (desirably about 0.05 mg to 2000 mg, and more desirably about 0.5 mg to 1000 mg) one to ten times daily (preferably one to five times daily, more desirably one to three times daily). Administration may be given in cycles, such that there are periods during which time niclosamide is not administered. This period could be, for example, about a day, a week, a month, or a year or more.

Rectal Administration

For compositions adapted for rectal use for preventing infection, a somewhat higher amount of a compound is usually preferred. Thus a dosage of a niclosamide is about 0.5 mg to 2500 mg per dose (preferably about 0.5 mg to 1500 mg) administered one to four times daily. Treatment durations are as described for oral administration.

Parenteral Administration

For intravenous or intramuscular administration of niclosamide, a dose of about 0.01 mg/kg to about 50 mg/kg body weight per day is recommended, a dose of about 0.05 mg/kg to about 15 mg/kg is preferred, and a dose of 0.1 mg/kg to 5 mg/kg is most preferred.

A compound can be administered daily for up to about 6 to 12 months or more. It may be desirable to administer a compound over a one to three hour period; this period may be extended to last 24 hours or more.

Inhalation

For inhalation, niclosamide is administered at a dose of about 0.001 mg to 5000 mg daily, and preferably at a dose of about 0.5 mg to 2000 mg daily.

Percutaneous Administration

For topical administration of niclosamide, a dose of about 1 mg to about 5 g administered one to ten times daily for one week to 12 months is usually preferable.

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the methods and compounds claimed herein are performed, made, and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention.

Experimental Procedures

Cell Lines Used

A549 human non-small cell lung carcinoma cell line (ATCC No. CCL-185) was maintained in Dulbecco's modified eagle medium (DMEM) supplemented with 10% FBS, 2 mM glutamine, 1% penicillin, 1% streptomycin and maintained at 37°C in the presence of 5% CO_2. HCT116 human colorectal carcinoma (ATCC No. CCL-247) was grown at 37°C in the presence of 5% CO_2

in McCoy's 5A medium supplemented with 10% FBS, 2 mM glutamine, 1% penicillin, and 1% streptomycin. DU145 human prostatic carcinoma cell line (ATCC No. HTB-81) was grown at 37°C in the presence of 5% CO_2 in minimum essential medium Eagle supplemented with 10% FBS, 2 mM glutamine, 0.1 mM non-essential amino acids, 1.0 mM sodium pyruvate, 1% penicillin, and 1% streptomycin. SKOV-3 human ovarian adenocarcinoma cell line was grown at 37°C and 5% CO_2 in McCoy's 5A medium supplemented with 10% FBS, 2 mM glutamine, 1% penicillin, and 1% streptomycin. MCF7 human breast adenocarcinoma cell line (ATCC No. HTB-22) was grown at 37°C and 5% CO_2 in minimum essential medium Eagle supplemented with 10% FBS, 2 mM glutamine 0.1 mM non-essential amino acids, 1.0 mM sodium pyruvate, 0.01 mg/mL bovine insulin, 1% penicillin, and 1% streptomycin. Cells were used at a density of 3000 cells per well.

Compounds and Compound Preparation

The following compounds were used: niclosamide, paclitaxel, chlorpromazine and etoposide (all from Sigma Chemical Co.; St. Louis,MO) and irinotecan and gemcitabine (obtained from Rosen Pharmacy, Belmont MA). Single agent dilutions of antiproliferative agents were used as a positive control and dilution vehicle (DMSO) was used as the untreated control. Stock solutions of each compound were prepared in DMSO and stored at–20°C with the exception of irinotecan, which was prepared in a solution of saline. Briefly, 1000-fold stock solutions were prepared for dilutions of each single test agent in DMSO in 384 well plates. In the experiments summarized in Tables 3-16 and 18, the dilutions were prepared by manual pipetteing in a non-linear series and dispensed into 384 well plates. The results shown in Table 18 were generated from dilutions prepared from the stock solution and dispensed using a Tomtech Quadra automated liquid handling station (Hamden, CT).

Anti-proliferation Assay

Combination matrices (two blocks per plate) were generated by combining one microliter of 1000-fold stockfrom each well in one master stock X-plate and one master stock Y-plate into one 384 well plate containing 100 μL of media and mixed to homogeneity to create a 10-fold stock of combination dose matrices in culture medium. Compound combination dilution plates were used fresh and discarded immediately after use. The 10-fold stock solution (6.6 μL) was transferred to an assay plate containing 40 μL of media. Cells were liberated from each culture flask with 2 mL of 0.25% trypsin and diluted into fresh culture medium at a density that would allow 3000 cells per well to be added in a total volume of 20 μL. Duplicate assay plates were generated and assay plates were incubated at 37°C in the presence of 5% CO_2 in a humidified incubator for 90-95 hours prior to cell viability assays. At 90-95 hours post compound addition, Alamar Blue was diluted to a final concentration of 20% in culture medium and added to each well to give a final concentration of 5% in 91.60 μL. Assay plates were incubated for four hours at 37°C in the presence of 5% CO_2 in a humified incubator. Metabolism of the Alamar Blue dye was analyzed by quantitating the amount of fluorescence intensity in each well. Quantitation using an LJL Analyst AD reader (LJL Biosystems, LJL Analyst AD serial # AD2038; Sunnyvale, CA) was taken at the middle of the well, with high attenuation, a 100 millisecond read time, and a filter with excitation at 530 nm and emission at 575 nm. Quantitation using Wallac Victor^2 readers (Perkin Elmer, Inc., Wallac 2 serial # 4202125; Wallac 4 serial # 4202289; Shelton, CT) was taken at the top of the well with stabilized energy lamp control, a 100 millisecond read time, and a filter with excitation at 530 nm and emission at 590 mm.

Determination of Inhibition

Percent inhibition (%I) for each well was calculated using the formula:

%I = ((average untreated wells – treated well)/average untreated wells)*100

The average untreated wells were calculated from the arithmetic mean of 40 wells on the plate treated with dilution vehicle only.

Bone Marrow Assay

Cryopreserved human bone marrow mononuclear cells were obtained from BioWhitaker (catalog # 2M-125C) and thawed according to the manufacturer's instructions. Bone marrow colony forming assays were performed in methylcellulose using a kit from Stem Cell Technologies (catalogue # 04464) according to the manufacturer's instructions. Briefly, 6×10^4 human bone marrow mononuclear cells were added to each methylcellulose aliquot provided in the kit. Compounds were diluted from high concentration stocks in DMSO to generate 10 x stocks in Iscove's DMEM containing 2% FBS and added to methylcellulose aliquots to give the indicated final concentrations. DMSO was used as an untreated control. Two replicate assay plates each containing 1.1 mL of methylcellulose, cells, and compounds were generated for each compound concentration condition. Assay plates were incubated in the presence of compounds at 37°C in the presence of 5% CO_2 to allow colony formation. The number of colonies was quantified at 16-20 days by visual inspection; only colonies containing 20 or more cells were counted. The total number of colonies for each set of plate replicates was calculated. Then data are presented as percent inhibition of colony formation compared to untreated control (DMSO only). Percent inhibition of colony formation was calculated by the following formula:

100*((untreated colonies – treated colonies)/untreated colonies).

Example 1: Antiproliferative Activity of Niclosamide.

The results from a non-linear dilution series of niclosamide on several human cancer cell lines are shown in Fig. 1. The tested cell lines were: A549 non-small cell lung carcinoma cells; HCT116 colorectal carcinoma cells; MCF7 breast tumor cells; DU145 prostatic carcinoma cells; and SKOV ovarian adenocarcinoma cells. Niclosamide exhibited antiproliferative activity against each of these cell lines *in vitro*; the estimated IC_{50} was between 400 and 900 nM. Moreover, at concentrations greater than 1 μM, greater than 80% inhibition was achieved against A549 cells and HCT116 cells. For each cell line, the data presented are the average of four trials, with the exception of the data for SKOV cells, which represents one trial.

The anti-proliferative effect demonstrated with the foregoing cell lines can be similarly demonstrated using other cancer cell lines, such as PA-1 ovarian teratocarcinoma, PANC-1 pancreatic ductal carcinoma, HT29 colorectal adenocarcinoma, H1299 large cell carcinoma, U-2 OS osteogenic sarcoma, U-373 MG glioblastoma, Hep-3B hepatocellular carcinoma, BT-549 mammary carcinoma, T-24 bladder cancer, C-33A cervical carcinoma, HT-3 metastatic cervical carcinoma, SiHa squamous cervical carcinoma, CaSki epidermoid cervical carcinoma, NCI-H292 mucoepidermoid lung carcinoma, NCI-2030, non small cell lung carcinoma, HeLa, epithelial cervical adenocarcinoma, KB epithelial mouth carcinoma, HT1080 epithelial fibrosarcoma, Saos-2 epithelial osteogenic sarcoma, PC3 epithelial prostate adenocarcinoma, SW480 colorectal carcinoma, CCL-228, and MS-751 epidermoid cervical carcinoma, and LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, UACC-257, and UACC-62 melanoma cell lines. The specificity can be tested by using cells such as NHLF lung fibroblasts, NHDF dermal fibroblasts, HMEC mammary epithelial cells, PrEC prostate epithelial cells, HRE renal epithelial cells, NHBE bronchial epithelial cells, CoSmC colon smooth muscle cells, CoEC colon endothelial cells, NHEK epidermal keratinocytes, and bone marrow cells as control cells.

Example 2: The Effect of Niclosamide and Gemcitabine on Bone Marrow Mononuclear Cells.

The therapeutic index (TI) is a relative measure of the effectiveness of an antiproliferative agent compared to its toxicity. Typically, the TI of an antiproliferative agent is expressed as a ratio of the dose required to achieve a particular anti-proliferative effect or endpoint (effective dose) to the dose that produces the maximum acceptable level of toxicity (maximum tolerable dose). The TI may be used as an index of the safety margin of a particular therapy. A therapy having a low TI must be monitored more carefully than one having a high TI. Patients receiving a low TI therapy are more prone to toxicity in the event of small overdosing or slight alterations in physiologic parameters that may result from normal interindividual variability. Therapies having a large TI are generally regarded as safer because larger deviations in dosage or interindividual variability are possible without producing unacceptable toxicity.

Many antiproliferative agents have low therapeutic indices. The difference between the dose required for effective antiproliferative therapy and that which causes unacceptable toxicity to the patient is small. The maximum dose of many antiproliferative agents is limited by the adverse effects caused by toxicity to non-neoplastic tissues. The cells of the bone marrow are often the most susceptible to intoxication. The dosage, frequency, and duration of antiproliferative therapy is frequently modified in response to deterioration of hematologic parameters such as an excessive loss of red blood cells, indicative of anemia, or a panleukopenia. Accordingly, there is a need for techniques that increase the TI of antiproliferative agents.

In order to evaluate the toxicity of niclosamide, a colony-forming assay of human bone marrow mononuclear cells was performed. In this assay, human bone marrow progenitor cells are allowed to proliferate in a semi-solid medium to form colonies. Toxicity of a test compound manifests itself as inhibition of the proliferation of these progenitors and prevention of colony formation. Colonies are easily quantified by visual inspection.

Niclosamide alone showed very low toxicity to human bone marrow – only 7% inhibition of colony formation at 1 μM, the highest concentration tested (Table 3). Gemcitabine inhibited 100% of colony formation at a dose of 20 μM. Niclosamide did not enhance the toxicity of gemcitabine against human bone marrow at any of the doses tested. Therefore, niclosamide can be used in conjunction with chemotherapeutic agents without enhancing the unwanted toxicity against bone marrow cells (Table 3).

Table 3

	Niclosamide (μM)				
Gemcitabine (μM)		1	0.5	0.1	0
	0.02	100.00	100.00	100.00	100.00
	0.005	80.29	83.43	83.43	87.66
	0.0025	9.76	11.79	25.60	0.18
	0	7.00	-5.34	-2.95	0.00

Example 3: Antiproliferative Activity of Niclosamide and Paclitaxel.

A549 Human Non-small Cell Lung Carcinoma Cells

The results from a non-linear dilution series of paclitaxel and niclosamide combinations on A549 cells are shown in Table 4. Paclitaxel IC_{50} is shifted from approximately 2 nM to approximately 0.5 nM in the presence of approximately 700 nM niclosamide. Niclosamide IC_{50} is shifted from approximately 700 nM to approximately 400 nM in the presence of 2 nM paclitaxel. The data presented are the average of four experiments.

Table 4

	Niclosamide (μM)									
Paclitaxel (μM)	1.5	1.0	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
0.500	95.22	91.07	89.81	90.24	89.79	89.94	89.28	89.86	89.42	90.14
0.100	94.27	91.01	89.85	88.95	89.11	87.69	86.81	85.92	86.40	87.13
0.020	95.64	92.62	90.52	91.70	84.96	85.93	81.55	82.82	79.62	88.92
0.005	96.35	88.76	90.16	72.10	81.45	69.49	70.95	64.52	78.31	67.91
0.004	94.82	93.07	79.90	85.66	83.45	74.09	72.31	75.65	55.80	79.88
0.003	95.50	90.11	87.35	64.98	83.00	49.62	73.53	48.04	70.24	58.36
0.002	95.41	87.18	70.91	72.69	40.28	60.74	16.87	64.40	52.70	59.79
0.001	95.68	83.19	77.14	67.72	47.10	19.65	24.69	-3.03	36.89	8.41
0.0005	93.73	83.35	62.10	43.78	31.24	20.12	1.53	-0.91	5.41	11.74
0	94.78	82.83	68.22	42.34	30.46	28.63	6.52	-4.77	7.65	7.85

HCT116 Human Colorectal Carcinoma Cells

The results from a hand pipetted dilution series of paclitaxel and niclosamide combinations on HCT116 cell growth are shown in Table 5. The IC_{50} of paclitaxel alone is approximately 3.5 nM. In the presence of 400 nM niclosamide, the IC_{50} of paclitaxel is reduced to 0.5 nM, a seven-fold reduction compared to paclitaxel alone. The data presented are the average of four experiments.

Table 5

	Niclosamide (μM)									
Paclitaxel (μM)	1.5	1.0	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
0.5	96.78	94.49	91.76	90.66	90.45	91.42	91.82	91.20	91.43	90.57
0.1	97.08	94.20	92.31	91.48	91.35	92.55	91.41	91.80	91.63	91.94
0.02	96.99	95.41	91.67	92.35	90.87	92.50	91.40	91.62	90.91	90.93
0.005	97.01	92.96	86.94	81.75	83.94	72.59	72.16	70.56	77.47	78.19
0.004	96.95	93.91	85.85	85.95	77.10	75.57	67.88	64.19	56.41	68.17
0.003	96.95	93.10	88.74	77.92	80.63	57.52	49.56	30.21	47.25	39.40
0.002	96.96	93.55	88.29	78.74	67.17	54.97	31.77	19.44	14.69	12.45
0.001	96.62	92.95	86.54	74.86	65.57	44.46	26.27	11.73	4.44	0.14
0.0005	96.91	93.74	86.94	75.58	69.43	54.36	25.99	14.50	2.92	1.77
0	97.10	93.76	87.62	85.04	74.99	54.33	39.20	15.36	7.77	4.50

DU145 Human Prostatic Carcinoma Cells

Table 6 shows the results from a hand pipetted dilution series of paclitaxel and niclosamide combinations on DU145 cell growth. The IC_{50} of paclitaxel alone is approximately 20 nM. In the presence of 800 nM niclosamide, the IC_{50} of paclitaxel is reduced to approximately 3 nM, a six-fold reduction compared to paclitaxel alone. The data presented are the average of four experiments.

Table 6

	Niclosamide (μM)										
Paclitaxel (μM)		1.5	1	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
	0.5	78.92	72.52	69.09	63.90	63.96	69.38	73.27	73.53	76.82	78.30
	0.1	77.43	71.59	66.87	63.66	54.11	62.34	66.74	70.31	72.65	72.45
	0.02	76.16	68.45	57.20	44.55	33.82	38.45	41.62	37.27	51.66	53.54
	0.005	74.13	65.07	39.28	21.52	8.37	-3.57	-8.47	-9.77	-1.24	13.77
	0.004	73.96	68.90	45.18	18.31	13.42	-6.69	-11.24	0.73	-1.63	33.64
	0.003	76.62	57.73	52.02	24.11	6.52	-2.73	-10.46	-3.76	8.01	22.68
	0.002	72.34	59.05	42.39	12.13	6.62	-10.07	-10.38	-15.31	-14.47	15.48
	0.001	70.99	60.59	40.09	13.32	1.62	-6.97	-14.73	-19.89	-19.46	14.31
	0.0005	67.34	60.27	33.56	14.83	1.91	-10.00	-17.75	-16.55	-22.01	8.61
	0	67.62	60.58	35.05	8.82	2.38	-12.63	-14.90	-14.38	1.36	8.32

SKOV3 Human Ovarian Adenocarcinoma Cell Line

The results from a hand-pipetted dilution series of paclitaxel and niclosamide combinations on SKOV3 cell growth are shown in Table 7. Paclitaxel alone reaches a maximum inhibition of approximately 40%. In the presence of 400 nM niclosamide, the IC_{50} of paclitaxel is approximately 1 nM. The data presented are the average of four experiments.

Table 7

	Niclosamide (μM)										
Paclitaxel (μM)		1.5	1.0	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
	0.5	81.89	77.17	72.10	66.30	63.16	55.69	47.09	34.71	25.94	24.89
	0.1	81.31	76.79	71.33	65.38	62.04	56.48	47.81	38.48	27.92	30.45
	0.02	79.94	75.60	70.16	63.74	60.85	56.22	45.64	33.56	22.39	39.07
	0.005	83.26	72.60	71.83	60.86	58.85	49.99	40.02	26.05	17.62	12.51
	0.004	81.13	78.42	71.34	64.72	58.28	52.62	41.26	36.41	12.29	20.46
	0.003	84.99	79.76	74.30	63.37	60.81	60.46	42.34	28.30	9.22	7.69
	0.002	83.03	75.63	68.26	61.94	60.24	51.74	39.56	25.40	4.18	4.65
	0.001	79.71	72.84	66.95	61.28	57.13	51.67	40.30	24.72	0.98	0.96
	0.0005	74.27	74.66	62.87	65.18	57.42	55.58	41.27	26.43	3.91	6.41
	0	77.79	72.27	70.98	60.90	59.15	51.60	40.30	22.67	2.79	0.85

MCF7 Human Breast Tumor Cells

The results from a hand-pipetted dilution series of paclitaxel and niclosamide combinations on MCF7 cell growth are shown in Table 8. The IC_{50} of paclitaxel alone is approximately 20 nM. In the presence of 800 nM niclosamide the IC_{50} of paclitaxel is reduced to below 0.5 nM. The data presented are the average of four experiments.

Table 8

	Niclosamide (μM)										
Paclitaxel (μM)		1.5	1	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
	0.5	75.67	73.72	67.09	63.02	62.29	53.21	47.95	50.85	51.21	55.33
	0.1	76.25	75.15	68.69	65.55	65.83	56.09	50.68	48.61	50.82	53.89
	0.02	75.50	74.23	69.82	63.10	61.91	53.25	44.88	47.77	47.18	53.69
	0.005	75.88	74.46	70.40	61.35	56.39	46.80	31.63	41.71	37.93	40.87
	0.004	75.71	72.82	67.02	61.48	56.20	48.67	32.21	31.10	35.17	38.19
	0.003	77.67	73.30	70.20	61.07	56.89	42.52	25.78	19.83	31.33	41.68
	0.002	72.91	72.00	67.80	58.54	56.10	42.69	16.45	14.65	13.38	21.18
	0.001	76.17	72.50	68.64	60.57	56.40	38.79	14.22	-3.17	-2.46	-0.84
	0.0005	74.45	72.11	68.01	61.53	55.82	42.99	17.24	3.19	-6.02	12.28
	0	78.92	73.84	69.61	63.28	57.93	49.95	25.86	2.02	15.09	13.52

Example 4: Antiproliferative Activity of Niclosamide and Gemcitabine.

A549 Human Non-small Cell Lung Carcinoma Cells

The results from a non-linear dilution series of gemcitabine and niclosamide combinations on A549 cells are shown in Table 9. Gemcitabine IC_{50} is shifted from approximately 5 nM to approximately 1 nM in the presence of 600 nM niclosamide. Niclosamide IC_{50} is shifted from approximately 600 nM to approximately 300 nM in the presence of 5 nM gemcitabine. The data presented are the average of four experiments. The data presented are the average of four experiments.

Table 9

	Niclosamide (μM)									
Gemcitabine (μM)	1.5	1.0	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
0.020	94.93	89.49	87.79	89.06	89.33	90.57	89.85	91.10	90.78	90.93
0.015	94.33	86.66	84.48	86.83	87.95	87.81	89.26	89.69	89.74	89.25
0.01	94.68	94.37	82.59	89.58	88.10	92.95	86.49	91.39	86.18	92.57
0.0075	95.46	87.01	86.19	81.93	85.96	68.52	90.21	73.26	87.57	66.57
0.005	95.79	93.95	81.77	89.39	72.52	71.44	53.60	76.46	52.89	61.26
0.0035	96.05	89.08	83.70	66.92	64.75	26.36	40.67	42.21	35.67	31.63
0.002	95.78	89.42	84.00	73.18	35.91	53.22	13.30	41.10	-13.45	35.42
0.0015	96.41	88.48	89.61	76.40	43.18	37.07	39.25	18.29	26.82	11.89
0.001	94.43	86.47	69.46	57.22	43.64	18.63	3.79	-5.35	-2.49	-0.72
0	95.32	85.29	76.40	55.37	46.28	21.36	7.95	-4.99	-2.99	-5.64

HCT116 Human Colorectal Carcinoma Cells

The results from a hand-pipetted dilution series of gemcitabine and niclosamide combinations on HCT116 cell growth are shown in Table 10. The IC_{50} of gemcitabine alone is approximately 4 nM. In the presence of 400 nM niclosamide, the IC_{50} of gemcitabine is reduced to approximately 1 nM, a four-fold reduction compared to gemcitabine alone. The data presented are the average of four experiments.

Table 10

	Niclosamide (μM)										
Gemcitabine (μM)		1.5	1.0	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
	0.02	96.88	92.48	88.67	85.90	86.67	89.59	89.63	89.46	88.78	91.01
	0.015	97.13	92.28	87.87	84.55	87.12	83.61	86.79	88.59	88.73	90.53
	0.01	97.03	94.70	87.72	87.32	81.84	83.86	79.72	83.28	80.77	86.42
	0.0075	97.15	93.70	90.21	85.32	83.05	75.12	82.91	64.00	69.46	77.12
	0.005	97.09	93.64	86.99	85.25	78.26	65.72	45.26	59.85	41.22	66.22
	0.0035	97.26	92.32	91.93	76.06	80.37	47.94	31.09	20.36	12.39	26.64
	0.002	96.99	94.01	85.40	74.59	65.89	45.79	28.14	15.93	5.89	1.20
	0.0015	96.94	92.10	84.23	74.35	66.28	45.06	24.50	16.54	4.18	-0.32
	0.001	97.10	95.78	88.00	80.88	65.39	56.01	30.21	19.42	5.56	1.21
	0	96.95	94.36	87.40	74.29	69.46	49.45	31.33	15.84	5.78	1.34

MCF7 Human Breast Tumor Cells

The results from a hand-pipetted dilution series of gemcitabine and niclosamide combinations on MCF7 cell growth are shown in Table 11. The IC_{50} of gemcitabine alone is approximately 10 nM. In the presence of 500 nM niclosamide the IC_{50} of gemcitabine is reduced to approximately 1 nM, a ten-fold reduction compared to gemcitabine alone. The data presented are the average of four experiments.

Table 11

	Niclosamide (μM)										
Gemcitabine (μM)		1.5	1.0	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
	0.02	76.29	72.82	69.27	66.56	64.83	59.47	52.74	53.03	50.46	49.34
	0.015	72.30	73.73	69.90	60.93	64.58	53.61	49.08	42.92	47.20	63.75
	0.01	74.74	72.16	68.15	64.32	60.85	52.95	47.64	45.49	46.92	51.22
	0.0075	72.84	69.19	67.09	63.14	62.12	48.51	41.07	37.96	43.94	40.68
	0.005	73.49	72.18	66.20	59.00	59.27	41.81	42.90	40.81	34.57	41.11
	0.0035	73.43	69.48	67.97	61.83	54.98	41.98	27.86	14.14	33.08	16.21
	0.002	74.78	70.04	66.32	60.10	56.70	38.17	23.76	1.54	-14.47	0.01
	0.0015	73.00	67.75	63.42	54.67	53.81	38.03	11.88	-10.49	-23.55	-12.37
	0.001	70.14	69.83	59.78	61.96	46.52	45.52	8.20	2.57	-17.16	1.71
	0	73.20	67.27	65.10	55.01	50.48	32.67	8.73	-18.60	-10.95	-11.68

DU145 Human Prostatic Carcinoma Cells

Table 12 shows the results from a hand-pipetted dilution series of gemcitabine and niclosamide combinations on DU145 cell growth. Gemcitabine alone reaches a maximum of approximately 30 % inhibition at the highest concentration tested (20 nM). In the presence of 1 μM niclosamide, the IC_{50} of gemcitabine is less than 1 nM. The data presented are the average of four experiments.

Table 12

	Niclosamide (μM)										
Gemcitabine (μM)		1.5	1	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
	0.02	74.38	57.68	49.52	34.64	34.28	29.20	24.02	20.89	32.44	33.82
	0.015	74.43	60.84	47.16	26.89	24.34	7.90	2.03	7.45	7.59	29.32
	0.01	70.71	62.97	40.85	27.45	15.85	1.61	-6.01	-7.46	-7.07	7.76
	0.0075	69.99	61.60	40.59	15.73	12.47	-5.40	-10.44	-18.07	-12.65	1.38
	0.005	70.06	60.40	39.61	16.31	8.68	-3.76	-12.19	-16.45	-21.18	0.33
	0.0035	71.78	64.04	42.82	18.48	12.01	-5.81	-1.26	-12.31	-9.97	-1.32
	0.002	70.24	61.62	39.98	14.42	8.78	-5.61	-19.37	-19.36	-21.71	2.77
	0.0015	70.19	60.07	38.20	16.51	8.05	-3.78	-14.89	-19.85	-18.79	4.02
	0.001	68.55	59.43	31.79	17.17	5.54	-3.96	-12.25	-20.00	-19.42	15.64
	0	68.78	59.31	27.91	10.01	2.67	-10.86	-17.19	-25.49	-22.58	-0.36

Example 5: Antiproliferative Activity of Niclosamide and Chlorpromazine.

A549 Human Non-small Cell Lung Carcinoma Cells

The results from a non-linear dilution series of chlorpromazine and niclosamide combinations on A549 cells are shown in Table 13. Chlorpromazine IC_{50} is shifted from approximately 10 μM to approximately 4 μM in the presence of 500 nM niclosamide. Niclosamide IC_{50} is shifted from approximately 600 nM to approximately 100 nM in the presence of 10.5 μM chlorpromazine. The data presented are the average of four experiments.

Table 13

	Niclosamide (μM)									
Chlorpromazine (μM)	1.5	1.0	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
22.5	97.38	97.17	96.41	95.25	94.86	94.25	93.99	92.04	87.65	88.53
20.0	97.24	96.41	94.64	93.01	92.69	91.31	89.53	86.45	86.13	86.10
16.0	96.97	96.98	93.90	93.57	88.96	92.01	84.90	91.42	82.16	86.75
12.0	97.18	94.21	93.63	86.63	88.56	81.66	86.24	64.40	77.07	70.79
10.5	96.82	95.79	90.05	89.09	86.83	85.52	72.97	61.55	56.71	72.85
9.0	96.75	92.20	90.75	84.32	82.56	71.15	60.88	36.78	54.09	47.69
7.5	96.85	92.73	85.16	83.08	68.44	58.93	31.90	50.21	25.82	36.00
6.0	96.78	89.11	83.52	71.89	64.20	36.83	30.31	10.03	21.82	10.00
4.0	95.90	88.06	77.85	65.24	49.06	30.35	6.52	3.63	-0.22	6.00
0	94.66	84.16	73.25	53.76	38.37	14.75	7.31	-7.00	-0.50	-0.89

HCT116 Human Colorectal Carcinoma Cell Line

The results from a hand-pipetted dilution series of chlorpromazine and niclosamide combinations on HCT116 cell growth are shown in Table 14. The IC_{50} of chlorpromazine alone is approximately 14 μM. In the presence of 400 nM niclosamide, the IC_{50} of chlorpromazine is reduced to approximately 5 μM, a three-fold reduction compared to that of chlorpromazine alone. The data presented are the average of four experiments.

Table 14

		Niclosamide (μM)									
Chlorpromazine (μM)		1.5	1.0	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
	22.5	96.47	96.42	95.98	96.21	95.63	91.49	85.76	83.64	77.57	80.79
	20.0	96.32	96.50	96.12	95.86	94.31	89.60	84.38	82.63	78.91	77.45
	16.0	96.53	96.50	96.18	96.12	92.02	87.58	81.84	77.40	63.87	69.82
	12.0	96.27	96.00	95.74	95.77	89.56	77.02	69.12	41.42	41.92	36.25
	10.5	96.62	96.18	96.21	95.08	89.50	79.66	79.72	51.55	31.59	36.89
	9.0	96.33	95.59	95.80	94.25	88.41	80.72	52.05	51.72	16.11	21.53
	7.5	96.59	96.53	96.18	95.28	85.00	69.00	44.10	27.65	13.56	11.25
	6.0	95.89	96.53	95.88	95.71	84.59	55.18	46.28	22.68	14.60	3.40
	4.0	95.95	96.18	96.07	93.03	77.27	71.30	31.56	16.96	8.46	4.19
	0	96.27	96.03	95.54	91.65	79.66	60.03	46.03	18.49	8.19	0.94

MCF7 Human Breast Tumor Cells

The results from a hand-pipetted dilution series of chlorpromazine and niclosamide combinations on MCF7 cell growth are shown in Table 15. Chlorpromazine alone reaches a maximum inhibition of approximately 40 % at the highest concentration used (22.5 μM). In the presence of 500 nM niclosamide the IC_{50} of chlorpromazine is approximately 5 μM. The data presented are the average of four experiments.

Table 15

	Niclosamide (μM)										
Chlorpromazine (μM)		1.5	1.0	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
	22.5	71.40	71.19	72.47	70.76	67.35	67.14	62.87	50.91	46.22	39.60
	20.0	73.11	70.97	69.91	65.00	65.21	60.73	53.69	44.51	38.75	37.89
	16.0	69.48	68.84	65.86	64.78	59.03	56.68	49.21	31.49	28.50	34.05
	12.0	69.48	67.13	64.14	61.80	54.54	48.99	39.81	22.09	23.39	19.75
	10.5	66.92	67.56	62.86	60.73	59.02	44.93	40.88	22.09	22.93	29.78
	9.0	68.63	66.28	62.44	62.65	60.30	53.25	33.19	25.09	16.32	22.32
	7.5	65.86	65.86	60.30	56.46	55.82	43.44	26.16	18.25	6.94	13.34
	6.0	66.07	66.92	61.80	58.60	51.76	35.33	28.07	8.02	11.41	13.34
	4.0	66.92	64.57	61.59	62.44	48.78	41.09	19.96	16.75	-4.79	17.60
	0	68.20	63.29	63.72	61.58	55.18	34.68	19.32	7.58	-1.81	-1.17

DU145 Human Prostatic Carcinoma Cell Line

Table 16 shows the results from a hand-pipetted dilution series of chlorpromazine and niclosamide combinations on DU145 cell growth. Chlorpromazine alone reaches a maximum of approximately 25 % inhibition at the highest concentration tested (22.5 μM. In the presence of 400 nM niclosamide, the IC_{50} of chlorpromazine is 9 μM. The data presented are the average of four experiments.

Table 16

	Niclosamide (μM)									
Chlorpromazine (μM)	1.5	1	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
22.5	88.97	87.48	86.05	83.65	80.84	77.12	56.23	29.41	18.77	22.54
20	87.63	87.08	85.05	83.89	79.38	73.91	42.53	29.19	13.75	24.98
16	86.42	86.56	82.80	81.13	78.17	68.48	55.09	15.61	5.01	16.76
12	85.17	84.65	78.78	76.80	73.41	59.63	29.12	6.20	-3.58	9.68
10.5	83.34	83.38	78.06	76.44	73.49	40.34	35.11	-0.22	-1.48	10.83
9	82.79	83.20	80.30	76.93	72.05	54.81	22.04	4.56	-8.69	11.54
7.5	83.86	82.91	76.23	74.89	69.34	43.46	20.17	-10.16	-2.64	9.93
6	82.48	80.86	78.17	76.77	64.81	35.48	16.41	-11.25	-12.77	7.93
4	80.98	81.53	78.77	76.31	62.76	41.87	14.76	-7.29	-8.58	4.44
0	82.13	80.12	78.26	74.43	61.56	34.06	4.44	-2.58	-7.66	8.00

Example 6: Antiproliferative Activity of Niclosamide and Etoposide.

The results from a 2-fold dilution series of etoposide and niclosamide combinations on A549 cells are shown in Table 17. Etoposide IC_{50} is shifted from approximately 2.5 μM to approximately 1.25 μM in the presence of 1.5 μM niclosamide. Niclosamide IC_{50} is shifted from approximately 1.5 μM to approximately 380 nM in the presence of 2.5 μM etoposide. Additionally, the combination of maximal dosages of niclosamide and etoposide resulted in greater antiproliferative activity (91.9%), compared to the maximal test dosages of each agent alone. The data presented are the average of four experiments.

Table 17

	Niclosamide (μM)										
Etoposide (μM)		6.100	3.050	1.525	0.763	0.381	0.191	0.095	0.048	0.024	0.000
	10.000	91.88	83.58	81.37	80.17	80.57	81.14	81.59	79.72	80.86	80.57
	5.000	85.80	74.66	67.68	68.36	63.02	67.34	62.22	58.30	61.94	65.69
	2.500	84.32	70.80	65.52	60.29	55.86	57.68	50.46	47.06	58.93	58.53
	1.250	81.25	64.21	53.53	49.27	46.32	48.82	45.07	44.50	40.30	34.73
	0.625	78.92	63.81	56.03	48.53	44.50	41.26	33.88	36.55	29.50	23.08
	0.313	79.61	62.28	52.23	46.49	40.13	40.18	29.79	21.49	25.36	10.76
	0.156	83.19	64.78	56.43	41.83	30.75	27.57	12.69	16.32	22.17	17.01
	0.078	80.29	60.52	51.09	39.39	32.40	25.64	11.38	8.88	23.82	-2.88
	0.039	79.55	62.62	52.05	38.19	26.66	25.81	11.55	-6.91	14.56	3.49
	0.000	80.91	61.54	54.78	30.35	15.02	7.01	-4.47	-8.84	-13.33	-22.76

Example 7: Antiproliferative Activity of Niclosamide and Irinotecan.

The results from a non-linear dilution series of irinotecan and niclosamide combinations on A549 cells are shown in Table 18. Irinotecan IC_{50} is shifted from approximately 100 nM to approximately 20 nM in the presence of 700 nM niclosamide. Niclosamide IC_{50} is shifted from approximately 700 nM to approximately 400 nM in the presence of 80 nM irinotecan. The data presented are the average of four experiments.

Table 13

	Niclosamide (μM)										
Irinotecan (μM)		1.5	1	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0
	2.500	96.92	95.00	93.58	92.26	91.74	91.75	91.12	91.33	91.57	90.60
	1.250	96.10	92.95	90.43	86.90	86.17	85.90	84.92	84.46	83.27	81.04
	0.625	95.91	91.08	86.14	87.10	85.02	85.45	79.17	77.21	75.89	80.96
	0.313	95.73	88.47	83.42	72.96	79.79	72.34	72.92	69.62	75.56	75.12
	0.156	95.24	90.71	74.31	83.26	68.83	85.05	76.54	78.11	68.89	68.02
	0.078	95.26	88.53	81.08	56.70	66.69	50.75	61.64	56.38	66.97	41.21
	0.039	94.62	88.55	68.55	66.79	54.01	36.57	26.51	31.05	34.33	18.77
	0.020	94.78	81.38	67.13	36.47	26.80	17.64	11.53	6.98	18.67	19.32
	0.010	93.22	79.20	59.75	46.55	33.73	36.76	7.53	25.30	13.61	10.37
	0	92.87	79.40	63.09	35.54	27.60	15.22	10.87	-0.29	12.53	7.18

The anti-proliferative effect demonstrated with the foregoing cell lines can be similarly demonstrated using other cancer cell lines, such as PA-1 ovarian, PANC-1 pancreatic ductal carcinoma, teratocarcinoma, HT29 colorectal adenocarcinoma, H1299 large cell carcinoma, U-2 OS osteogenic sarcoma, U-373 MG glioblastoma, Hep-3B hepatocellular carcinoma, BT-549 mammary carcinoma, T-24 bladder cancer, C-33A cervical carcinoma, HT-3 metastatic cervical carcinoma, SiHa squamous cervical carcinoma, CaSki epidermoid cervical carcinoma, NCI-H292 mucoepidermoid lung carcinoma, NCI-2030, non small cell lung carcinoma, HeLa, epithelial cervical adenocarcinoma, KB epithelial mouth carcinoma, HT1080 epithelial fibrosarcoma, Saos-2 epithelial osteogenic sarcoma, PC3 epithelial prostate adenocarcinoma, SW480 colorectal carcinoma, CCL-228, and MS-751 epidermoid cervical carcinoma, and LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, UACC-257, and UACC-62 melanoma cell lines. The specificity can be tested by using cells such as NHLF lung fibroblasts, NHDF dermal fibroblasts, HMEC mammary epithelial cells, PrEC prostate epithelial cells, HRE renal epithelial cells, NHBE bronchial epithelial cells, CoSmC colon smooth muscle cells, CoEC colon endothelial cells, NHEK epidermal keratinocytes, and bone marrow cells as control cells.

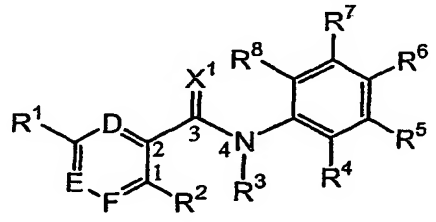
Other Embodiments

All publications and patents mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention that are obvious to those skilled in oncology or related fields are intended to be within the scope of the invention.

What is claimed is:

Claims

1. A method for treating a patient who has a neoplasm, said method comprising administering to said patient a compound having the formula I:



I

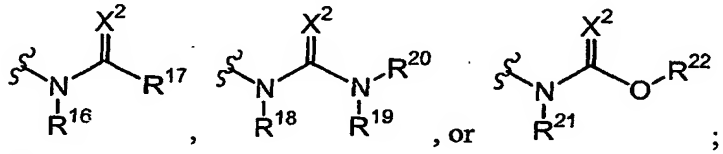
or a salt thereof, wherein

D is N or CR^9;

E is N or CR^{10};

F is N or CR^{11};

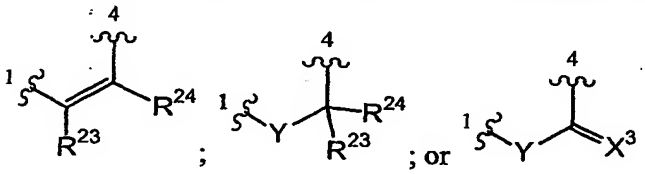
R^1 is H, halide, OR^{12}, SR^{13}, $NR^{14}R^{15}$,



;

R^2 is H, OH, or OR^{12};

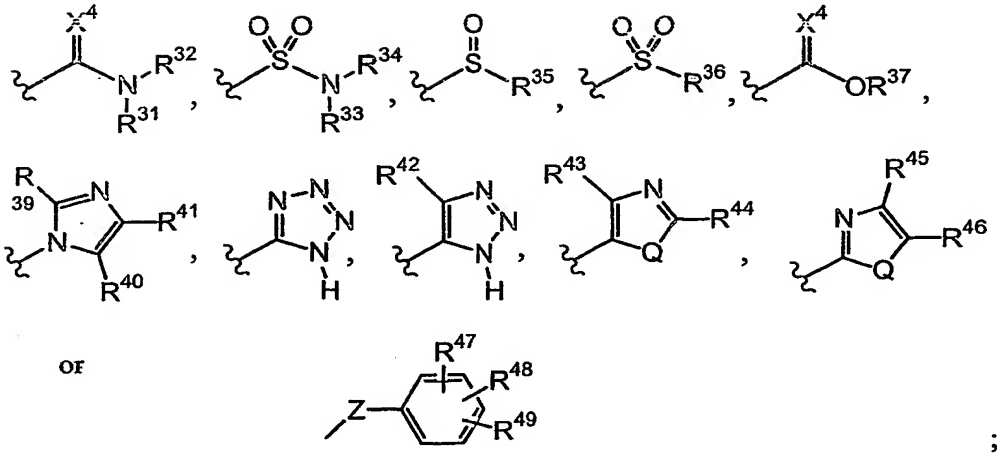
R^3 is H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; or R^2 and R^3 combine to form a six-membered ring in which position 1 is connected to position 4 by



;

R^4 and R^8 are each, independently, selected from H, halide, CF_3, OR^{28}, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl;

R^5, R^6, and R^7 are each, independently, selected from H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl, halide, NO_2, CO_2H, SO_3H, CF_3, CN, OR^{29}, SR^{30},



or

;

each X^1, X^2, X^3, and X^4 is, independently, O S; or NR^{38};

Y is $CR^{25}R^{26}$, O, S, or NR^{27};

Z is O, S, or $CR^{50}R^{51}$;

each Q is, independently, O, S, or NR^{52};

R^9, R^{10}, and R^{11} are each, independently, H, OH, OR^{12}, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-7} heteroalkyl, halide, or NO_2;

R^{12} and R^{13} are each, independently, acyl, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl;

R^{17}, R^{22}, R^{35}, R^{36}, R^{37}, R^{38}, and R^{52} are each, independently, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl;

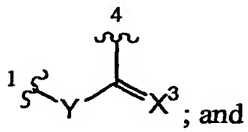
R^{14}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, and R^{47} are each, independently, H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl;

R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, and R^{51} are each, independently, H, halide, CN, NO_2, CF_3, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl,

wherein said compound is administered in an amount effective to inhibit growth of said neoplasm.

2. The method of claim 1, wherein X^1 is an oxygen atom; R^2 is OH; and R^3 is H.

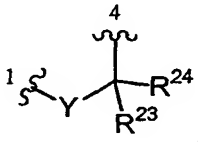
3. The method of claim 1, wherein X^1 is an oxygen atom; R^2 and R^3 combine to form a six-membered ring in which position 1 is connected to position 4 by



; and

Y is an oxygen atom.

4. The method of claim 1, wherein X^1 is an oxygen atom; R^2 and R^3 combine to form a six-membered ring in which position 1 is connected to position 4 by



; and

Y is an oxygen atom.

5. The method of claim 1, wherein X^1 is an oxygen atom; R^2 is OH; D is CR^9; E is CR^{10}; F is CR^{11}; R^1 is halide; R^{11} is hydrogen or halide; and R^3, R^9, and R^{10} are H.

6. A method for treating a patient who has a neoplasm, said method comprising administering to said patient a compound selected from the group consisting of niclosamide, oxyclozanide, closantel, rafoxanide, resorantel, clioxanide, tribromsalan, dibromsalan, brotianide, 4'-chloro-3-nitrosalicylanilide, 4'-chloro-5-nitrosalicylanilide, 2'-chloro-5'-methoxy-3-nitrosalicylanilide, 2'-methoxy-3,4'-dinitrosalicylanilide, 2',4'-dimethyl-3-nitrosalicylanilide, 4',5-dibromo-3-nitrosalicylanilide, 2'-chloro-3,4'-dinitrosalicylanilide, 2'-ethyl-3-nitrosalicylanilide, 2'-bromo-3-nitrosalicylanilide, and flusalan, or a salt thereof, wherein said compound is administered in an amount effective to inhibit growth of said neoplasm.

7. The method of claim 6, wherein said compound is niclosamide or a salt or ester thereof.

8. The method of claim 7, wherein said niclosamide salt is the ethanolamine, piperazine, or monohydrate salt of niclosamide.

9. A method for treating a patient who has a neoplasm, said method comprising administering to said patient a compound selected from the group consisting of ivermectin, abamectin, doramectin, moxidectin, mylbemycin D, niclofolan, praziquantel, diamphenethide, and chlorsulon.

10. The method of any of claims 1-9, wherein said method further comprises administering to said patient an antiproliferative agent, wherein said compound and said antiproliferative agent are administered simultaneously or within 14 days of each other, in amounts that together are effective to inhibit growth of said neoplasm.

11. The method of claim 10, wherein said antiproliferative agent is selected from the group consisting of paclitaxel, gemcitabine, etoposide, irinotecan, and chlorpromazine.

12. The method of claim 11, wherein said compound and said antiproliferative agent are administered within 10 days of each other.

13. The method of claim 12, wherein said compound and said antiproliferative agent are administered within 5 days of each other.

14. The method of claim 13, wherein said compound and said antiproliferative agent are administered within 24 hours of each other.

15. The method of claim 14, wherein said compound and said antiproliferative agent are administered within 1 hour of each other.

16. The method of claim 15, wherein said compound and said antiproliferative agent are administered simultaneously.

17. The method of any of claims 10-16, further comprising administering to said patient a second antiproliferative agent.

18. The method of claim 17, wherein second antiproliferative agent is administered simultaneously or within fourteen days of said compound and said antiproliferative agent.

19. The method of any of claims 1-18, wherein said neoplasm is cancer.

20. The method of claim 19, wherein said cancer is selected from the group consisting of acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, polycythemia vera, Hodgkin's disease, non-Hodgkin's disease, Waldenstrom's macroglobulinemia, heavy chain disease, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodenroglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

21. The method of claim 20, wherein said cancer is lung carcinoma, small cell lung carcinoma, breast cancer, colon cancer, or prostate cancer.

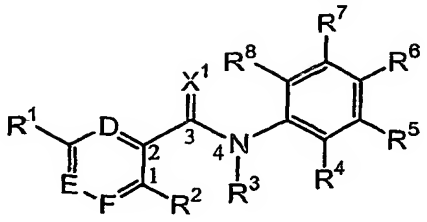
22. The method of any of claims 1-21, wherein said compound is administered in an amount between 0.1 and 3000 mg per day.

23. The method of claim 22, wherein said compound is administered in an amount between 0.5 and 2000 mg per day.

24. The method of any of claims 1-9, wherein said compound is administered in an amount that is not substantially toxic to bone marrow mononuclear cells.

25. The method of any of claims 10-16, wherein said compound is administered in an amount that, in combination with said antiproliferative agent, does not substantially increase the toxicity against bone marrow mononuclear cells, relative to toxicity of said antiproliferative agent against bone marrow mononuclear cells in the absence of said compound of formula (I).

26. A composition comprising: (i) a compound having the formula I:



I

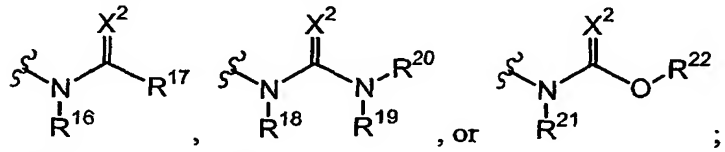
or a salt thereof, wherein

D is N or CR^9;

E is N or CR^{10};

F is N or CR^{11};

R^1 is H, halide, OR^{12}, SR^{13}, $NR^{14}R^{15}$,

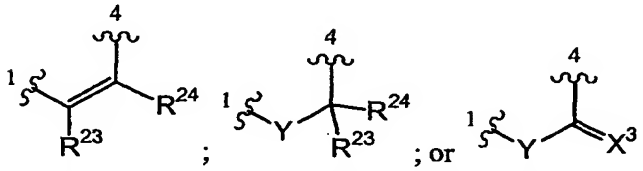


;

R^2 is H, OH, or OR^{12};

R^3 is H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_4-C_9 alkaryl, aryl, heteroaryl, or heterocyclyl; or

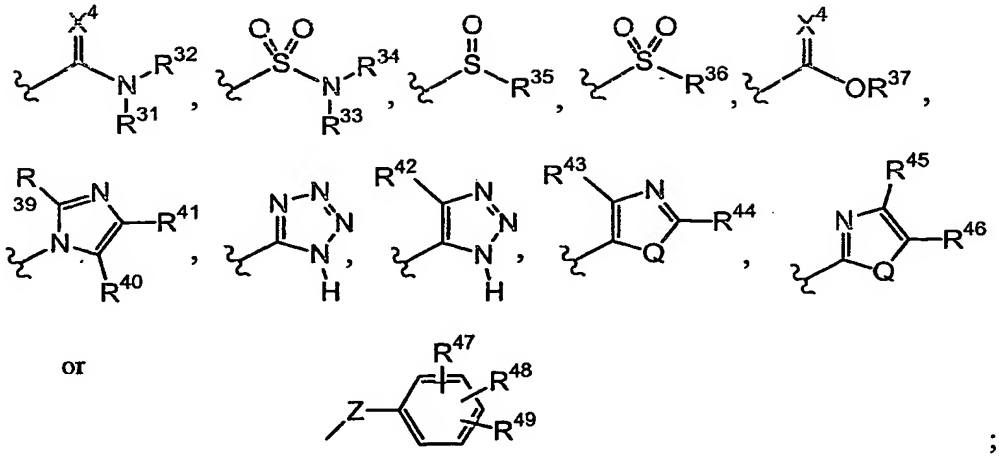
R^2 and R^3 combine to form a six-membered ring in which position 1 is connected to position 4 by



;

R^4 and R^8 are each, independently, selected from H, halide, CF_3, OR^{28}, C_1-C_6 alkyl, C_4-C_9 alkaryl, or C_1-C_6 heteroalkyl;

R^5, R^6, and R^7 are each, independently, selected from H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_4-C_9 alkaryl, aryl, halide, NO_2, CO_2H, SO_3H, CF_3, CN, OR^{29}, SR^{30},



or

;

each X^1, X^2, X^3, and X^4 is, independently, O S; or NR^{38};

Y is $CR^{25}R^{26}$, O, S, or NR^{27};

Z is O, S, or $CR^{50}R^{51}$;

each Q is, independently, O, S, or NR^{52};

R^9, R^{10}, and R^{11} are each, independently, H, OH, OR^{12}, C_1-C_6 alkyl, halide, or NO_2;

R^{12} and R^{13} are each, independently, C_1-C_6 acyl, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_4-C_9 alkaryl, aryl, heteroaryl, or heterocyclyl;

R^{17}, R^{22}, R^{35}, R^{36}, R^{37}, R^{38}, and R^{52} are each, independently, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_4-C_9 alkaryl, aryl, heteroaryl, or heterocyclyl;

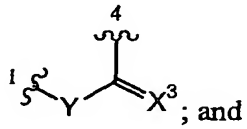
R^{14}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, and R^{47} are each, independently, H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_4-C_9 alkaryl, aryl, heteroaryl, or heterocyclyl;

R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, and R^{51} are each, independently, H, halide, CN, NO_2, CF_3, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_4-C_9 alkaryl, aryl, heteroaryl, or heterocyclyl; and

(ii) an antiproliferative agent.

27. The composition of claim 26, wherein X^1 is an oxygen atom; R^2 is OH; and R^3 are H.

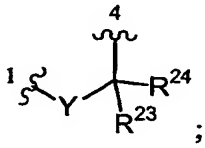
28. The composition of claim 26, wherein X^1 is an oxygen atom; R^2 and R^3 combine to form a six-membered ring in which position 1 is connected to position 4 by



; and

Y is an oxygen atom.

29. The composition of claim 26, wherein X^1 is an oxygen atom; R^2 and R^3 combine to form a six-membered ring in which position 1 is connected to position 4 by



; and

Y is an oxygen atom.

30. The composition of any of claims 26-29, wherein X^1 is an oxygen atom; R^2 is OH; D is CR^9; E is CR^{10}; F is CR^{11}; R^1 is halide; R^{11} is hydrogen or halide; and R^3, R^9, and R^{10} are H.

31. A composition comprising: (i) a compound selected from the group consisting of niclosamide, oxyclozanide, closantel, rafoxanide, resorantel, clioxanide, tribromsalan, dibromsalan, brotianide, 4'-chloro-3-nitrosalicylanilide, 4'-chloro-5-nitrosalicylanilide, 2'-chloro-5'-methoxy-3-nitrosalicylanilide, 2'-methoxy-3,4'-dinitrosalicylanilide, 2',4'-dimethyl-3-nitrosalicylanilide, 4',5-dibromo-3-nitrosalicylanilide, 2'-chloro-3,4'-dinitrosalicylanilide, 2'-ethyl-3-nitrosalicylanilide, 2'-bromo-3-nitrosalicylanilide, and flusalan, or a salt or ester thereof; and (ii) an antiproliferative agent.

32. The composition of claim 31, wherein said compound is niclosamide or a salt thereof.

33. The composition of claim 32, wherein said niclosamide salt is the ethanolamine, piperazine, or monohydrate salt of niclosamide.

34. A pharmaceutical composition comprising: (i) a compound which is an antihelminthic agent; and (ii) an antiproliferative agent.

35. The composition of claim 34, wherein said antihelminthic agent is selected from the group consisting of ivermectin, abamectin, doramectin, moxidectin, mylbemycin D, niclofolan, praziquantel, diamphenethide, and chlorsulon.

36. The composition of any of claims 26-35, wherein said antiproliferative agent is selected from the group consisting of paclitaxel, gemcitabine, etoposide, irinotecan, and chlorpromazine.

37. A method for identifying combinations of compounds useful for treating a patient having a neoplasm, said method comprising the steps of:

(a) contacting cancer cells *in vitro* with (i) niclosamide or an antiproliferative agent and (ii) a candidate compound; and

(b) determining whether the combination of said niclosamide or an antiproliferative and said candidate compound reduces growth of said cancer cells relative to cancer cells contacted with said niclosamide or an antiproliferative agent but not contacted with said candidate compound, or cancer cells contacted with said candidate compound but not with said niclosamide or an antiproliferative agent, wherein a reduction of said growth identifies said combination as a combination that is useful for treating a patient having a neoplasm.

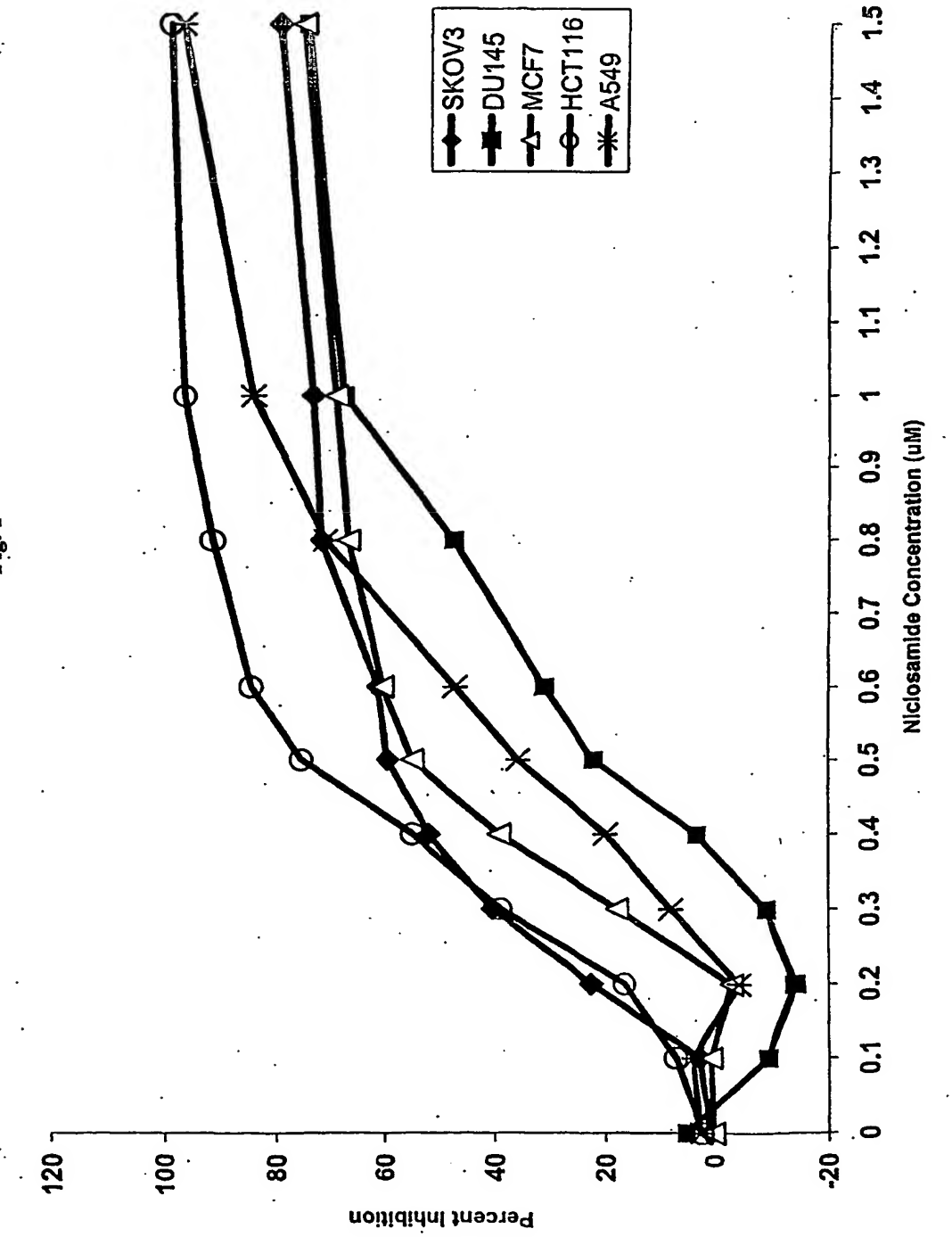

SKOV3
DU145
MCF7
HCT116
A549
Percent Inhibition
120
100
80
60
40
20
0
-20
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
1.2
1.3
1.4
1.5
Niclosamide Concentration (uM)

Fig. 1